DISSERTATION TITLED

"GLYCEMIC PROFILE OF PATIENTS ON HYDROXYCHLOROQUINE"

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CERTIFICATE

This is to certify that the dissertation entitled **"GLYCEMIC PROFILE OF PATIENTS ON HYDROXYCHLOROQUINE"** is a bonafide work done by **DR. A.MOHAMED ILIYAS**, Post Graduate Student, Institute of Internal Medicine, Madras Medical College, Chennai-3, in partial fulfillment of the University Rules and Regulations for the award of MD Branch – I General Medicine, under our guidance and supervision, during the academic year 2013 - 2016.

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DECLARATION

I solemnly declare that the dissertation entitled **"GLYCEMIC PROFILE OF PATIENTS ON HYDROXYCHLOROQUINE"** is done by me at Madras Medical College, Chennai - 3 during June 2015 to December 2015 under the guidance and supervision of **Prof. G. SUNDARAMURTHY**, **M.D.** to be submitted to The Tamilnadu Dr. M.G.R Medical University towards the partial fulfillment of requirements for the award of **M.D. DEGREE IN GENERAL MEDICINE BRANCH - I.**

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Last but not the least, I wish to thank all the patients without whom the study would have been impossible.

ABBREVIATIONS

ADA	**American Diabetes Association**
DM	**Diabetes Mellitus**
FBS	**Fasting Blood Glucose**
HbA1C	**Glycosylated Hemoglobin**
HCQ	**Hydroxychloroquine**
IGT	**Impaired Glucose Tolerance**
NGT	**Normal Glucose Tolerance**
PPBS	**Post Prandial Blood Glucose**
RA	**Rheumatoid Arthritis**
SLE	**Systemic Lupus Erythematosus**

CONTENTS

INTRODUCTION

INTRODUCTION

Diabetes mellitus is a group of metabolic disorders which are characterized by chronic hyperglycemia and associated disturbance in carbohydrate, fat, and protein metabolism because of absolute or relative deficiency in insulin secretion and/or action.[1]

The long standing effects of diabetes include nephropathy leading to renal failure, progressive development of retinopathy leading to potential blindness, features of autonomic dysfunction, sexual dysfunction, neuropathy leading to foot ulcers, charcoat joint, amputation. They are at increased risk of cerebrovascular, peripheral vascular and cardiovascular diseases compared to general population.

Due to delayed diagnosis, lack of awareness, inadequate control of the disease and hypertension, there is a high prevalence of diabetes related complications like retinopathy (18%), peripheral vascular disease (6.3%), peripheral neuropathy (26%), peripheral neuropathy (26%), overt nephropathy (2.2%) with 27% having microalbuminuria and coronary artery disease (21%).Lifestyle changes because of modernization and urbanization hasled to lack of physical activity, increased stress, unhealthy diet habits leading

to Obesity, Overweight with high level of insulin resistance.[2]

Diabetes is the most common metabolic disease that's is present in each and every part of the world. It is the major public health challenge in the 21st century. 80 to 90% of the diabetic population is constituted by type 2 diabetes. In developing countries including INDIA, chronic metabolic disorders pose an increased challenge to national health than the communicable diseases.[3-4]

AIMS

AND

OBJECTIVES

AIMS AND OBJECTIVES

1) To compare the glycemic profile of patients suffering from Rheumatological diseases before and after initiating treatment with Hydroxychloroquine.

2) To analyse the effect of Hydroxychloroquine on blood glucose and its potential use as an oral hypoglycemic agent in diabetes mellitus.

REVIEW

OF

LITERATURE

REVIEW OF LITERATURE

HISTORY OF DIABETES

Thomas Willis, an Anatomist, Physician and Professor of Natural Philosophy in Oxford University discovered diabetes in 1674 by tasting the urine of people with diabetes.[5] It was described way back in 400 B.C. by Susruta in India who described it as "HONEYED URINE".[6] In 1776, Matthew Dobson of Manchester, England demonstrated the presence of sugar in the urine of diabetic individuals by boiling the urine to note a crystalline residue. It had the appearance and taste of "BROWN SUGAR".[7]

It was thought that the kidneys are the major source of the problem, since the most striking symptoms and signs were related to polyuria. In 1788 Thomas Cawley reported shriveled pancreas with stones in an autopsy of a diabetic person. It must be the first published reference of diabetes relating the disease to the pancreas.[8]

Apollinaire Bouchardat and E. Lancearaux were the two strongest forces who argued for a pancreatic factor in the causality of diabetes. Subsequently Lanceraux and his students concluded that two types of diabetes exists namely "Diabete Maigre - Diabetes of Thin" and "Diabete Gras - Diabetes of Fat".[9] Joseph von Mering and Oscar Minkoswki in 1889 did total pancreatectomy on two

dogs and demonstrated polyuria. This was the turning point in history of diabetes. Laguesse in 1893 drew the attention to theforgotten original observations of Langerhans and suggested the collections of interacinar cells of pancreas as a secretory gland within pancreas. He later named them as islets of Langerhans.[10]

Between 1921 and 1922, Frederick Banting, a surgeon; Charles Best, a graduate student; John Macleod, a physiology professor And J. B. Collip, a skilled chemist went on to succeed infulfilling of all of the criteria for a therapeutic active insulin. They produced the first successful insulinpreparation in treating human diabetes.[11]In 1922, Banting and Macleod were awarded the Nobel Prize in Medicine. Leonard Thompson, a 14 year old boy was the first to receive the pancreatic extract named isletin then.

Multiple milestones have been achieved after Banting and Best's work. Sulfonylureas were the first oral hypoglycemic agents introduced in 1955. Alpha glucosidase inhibitors were widely used in 1980s. Thiazolidinediones were introduced subsequently in 1990s.

Glycosylated hemoglobin assay gained popularity and was widely used from the late 1970s. The property of glucose to bind to hemoglobin came to be noted in 1968, after the discovery by an

investigator who claimed that a group of his diabetic patients had a huge difference in minor hemoglobin fraction in an assay of electrophoresis.[12-13]

BURDEN OF DIABETES:

In INDIA, Diabetes Mellitus is fast gaining the status of a potential epidemic. It is home to more than 65 million diabetic people.[14-15] It is next to CHINA (98 million) and is followed by USA (24 million). 50% of the world's Diabetic population live in one of the above three countries, according to the International Diabetes Federation (2013). Earlier it was considered as a disease of high socio - economic people. It was more prevalent in urban India. But the present scenario suggests that the disease affects the low socio - economic people too. There is a marked rise in the incidence and prevalence of diabetes in rural India.

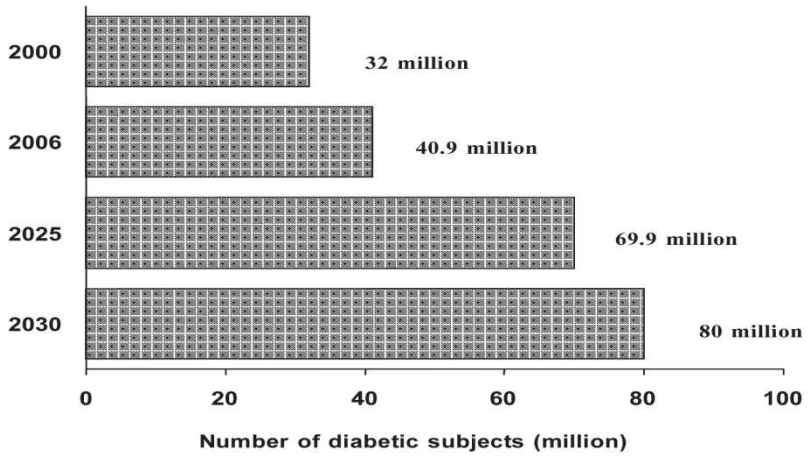
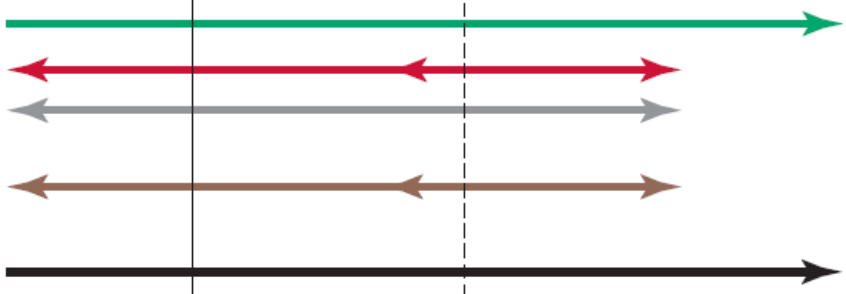


Fig. 1. Estimated number of diabetic subjects in India.

The highest prevalence of diabetes is reported from ERNAKULAM located in KERALA (19.5%). The lowest prevalence is reported from KASHMIR Valley (6.1%). In TAMILNADU, diabetes prevalence in cities amount to 16.4% while, peri - urban villages document 9.2%. The prevalence of diabetes in the rural areas of economically better regions of Tamilnadu, Chandigarh and Maharastra was 7.8%, 8.3% and 6.5% respectively.

WHO has estimated that there will be an increase in global expenditure for diabetes to 411 billion dollars in the next 20 years from 234 billion dollars in 2007. In INDIA the median expenditure has increased to 9000 rupees in 2005 from 4200 rupees in 1998. 25 to 30% of the poor people's income is spent on health care.[16] It further increases in coexisting diabetic complications.

SPECTRUM OF GLUCOSE HOMEOSTASIS AND DIABETES

Type of Diabetes	Normal glucose tolerance	Hyperglycemia		
		Pre-diabetes*	Diabetes Mellitus	
		Impaired fasting glucose or impaired glucose tolerance	Not insulin requiring	Insulin required for control	Insulin required for survival
Type 1 Type 2 Other specific types Gestational Diabetes Time (years)				
FPG	<5.6 mmol/L (100 mg/dL)	5.6–6.9 mmol/L (100–125 mg/dL)	≥7.0 mmol/L (126 mg/dL)	
2-h PG	<7.8 mmol/L (140 mg/dL)	7.8–11.0 mmol/L (140–199 mg/dL)	≥11.1 mmol/L (200 mg/dL)	
HbA1C	<5.6%	5.7–6.4%	≥6.5%	

ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS[17]

I.TYPE 1 DIABETES:

Destruction of beta cells, leading to absolute insulindeficiency.

A. Immune – mediated.

B. Idiopathic.

II. TYPE 2 DIABETES:

It can range from predominantly insulin secretory defect with insulin resistance to predominantly insulin resistance with relative insulin deficiency.

III. OTHER SPECIFIC TYPES OF DIABETES:

A. Genetic defect in beta cell development or function characterized by mutations in:

1. Hepatocyte nuclear transcription factor (HNF) 4α (**MODY 1**)
2. Glucokinase (**MODY 2**)
3. HNF-1α (**MODY 3**)
4. Insulin promoter factor-1 **(IPF-1**; **MODY 4**)
5. HNF-1β (**MODY 5**)
6. NeuroD1 (**MODY 6**)
7. Mitochondrial DNA

8. Subunits of ATP-sensitive potassium channel

9. Proinsulin or insulin

10. Other pancreatic islet proteins /regulators such as ***KLF11, GATA4, GATA6 PAX4, BLK,, SLC2A2*** **(GLUT2),** ***RFX6, GLIS3***

***MODY :** Maturity - Onset Diabetes of the Young.

B. Genetic defects in action of insulin.

1. Type A insulin resistance.

2. Leprechaunism.

3. Rabson – Mendenhall syndrome.

4. Lipodystrophy syndromes.

C. Diseases ofexocrinepancreas - pancreatitis, pancreatectomy,cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy, neoplasia, mutations in carboxyl ester lipase.

D. Endocrinopathies: Acromegaly, Cushing's syndrome, Glucagonoma, Pheochromocytoma, Somatostatinoma, Aldosteronoma.

E. Drug or chemical induced: Glucocorticoids, Pentamidine, Nicotinic acid, Vacor (a rodenticide), Diazoxide, Beta adrenergic agonists, Thiazides, Hydantoins, Asparaginase, Calcineurin and mTOR inhibitors, Alpha - interferons, Protease inhibitors, Epinephrine, Antipsychotics (atypicals and others).

F. Infections:

Congenital rubella, Coxsackievirus , Cytomegalovirus.

G. Uncommon forms of immune- mediated diabetes:

Anti - insulin receptor antibodies, “stiff-person” syndrome.

H. Genetic syndromes sometimes associated with diabetes:

Down’s syndrome, Klinefelter’s syndrome, Wolfram’s syndrome, Turner’s syndrome, Myotonic dystrophy, Friedreich’s ataxia, Huntington’s chorea,

Laurence - Moon - Biedl syndrome, Porphyria, Prader - Willi syndrome.

IV. Gestational Diabetes Mellitus (GDM)

The terms Insulin Dependent Diabetes Mellitus and Non – Insulin Dependent Diabetes Mellitus are obsolete now.

Monogenic Diabetes and Maturity onset diabetes of young (MODY) are subtype of Diabetes Mellitus.They are charecterised by Autosomal Dominant inheritance, impaired insulin secretion and early onset hyperglycemia usually less than 25 years.

GESTATIONAL DIABETES MELLITUS:

Pregnant mothers should be routinely screened at 24 - 28 weeks to detect GDM.

Carpenter and Coustan classification:

American Diabetes Association has adopted this and GDM is diagnosed if any 2 values cross the mentioned cut-off.

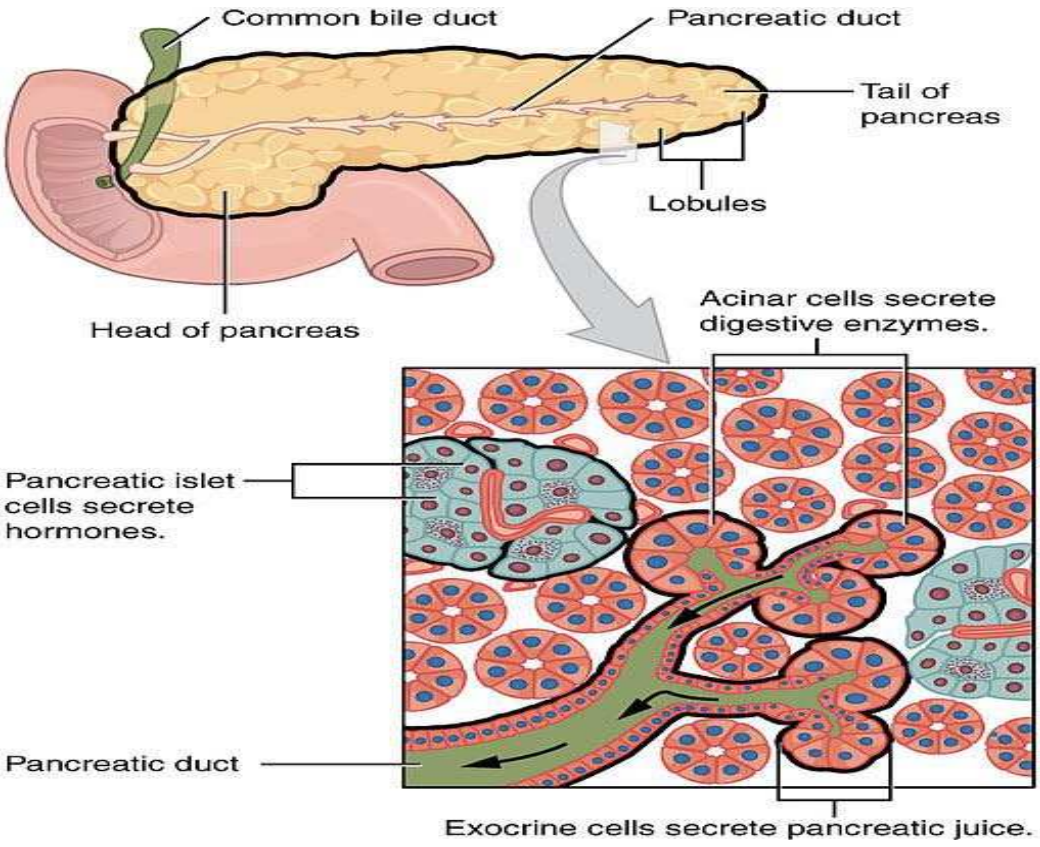
	100 g OGTT	75 g OGTT
Fasting	95 mg/dl	95 mg/dl
1 - hour	180 mg/dl	180 mg/dl
2 - hour	155 mg/dl	155 mg/dl
3 - hour	140 mg/dl	-

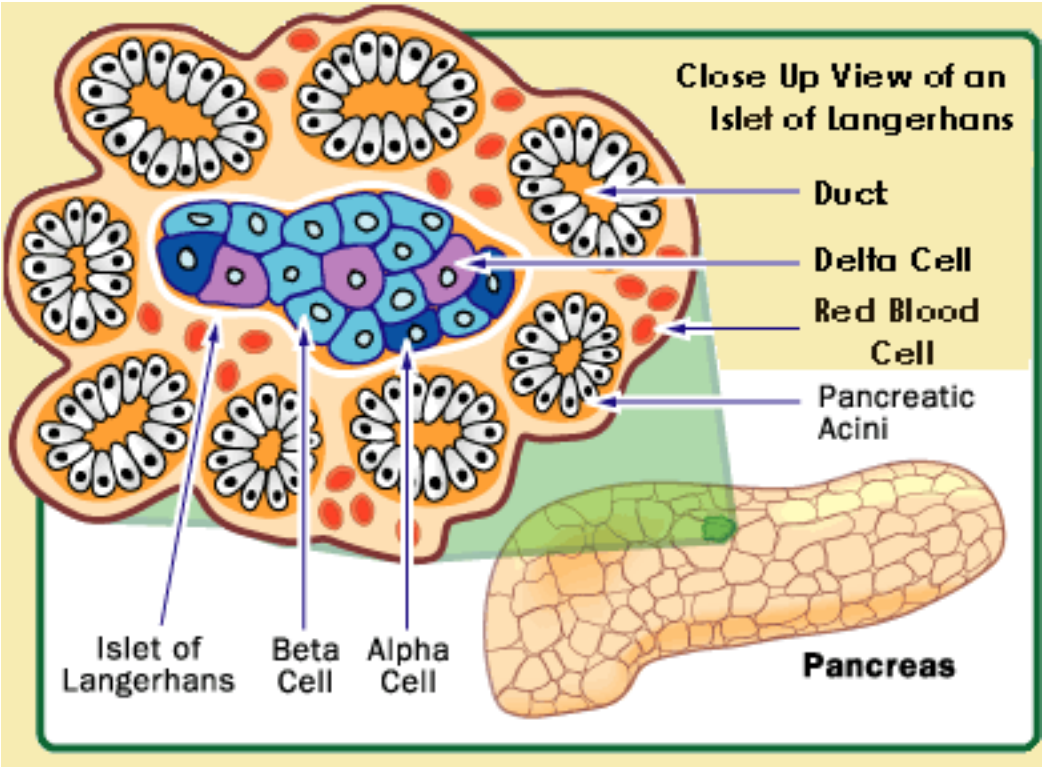
WHO Classification:

	Fasting plasma glucose	2 hour plasma glucose
IGT	-	140 - 199 mg/dl
Diabetes	≥126 mg/dl	≥200 mg/dl

ANATOMY AND PHYSIOLOGY OF PANCREAS:

Pancreas is a soft, lobulated, elongated and a retroperitoneal organ, wrapping around the second part of duodenum. It liestransversely at the level of L1 and L2. Its 15 - 20 cms long, 3 cm broad and 2 cm thick. It weighs around 90 grams. It derives its blood supply from splenic artery and pancreaticoduodenal arteries. It drains via splenic vein into portal vein. It has both sympathetic and parasympathetic nerve supply. It consists of both exocrine and endocrine parts. [18]



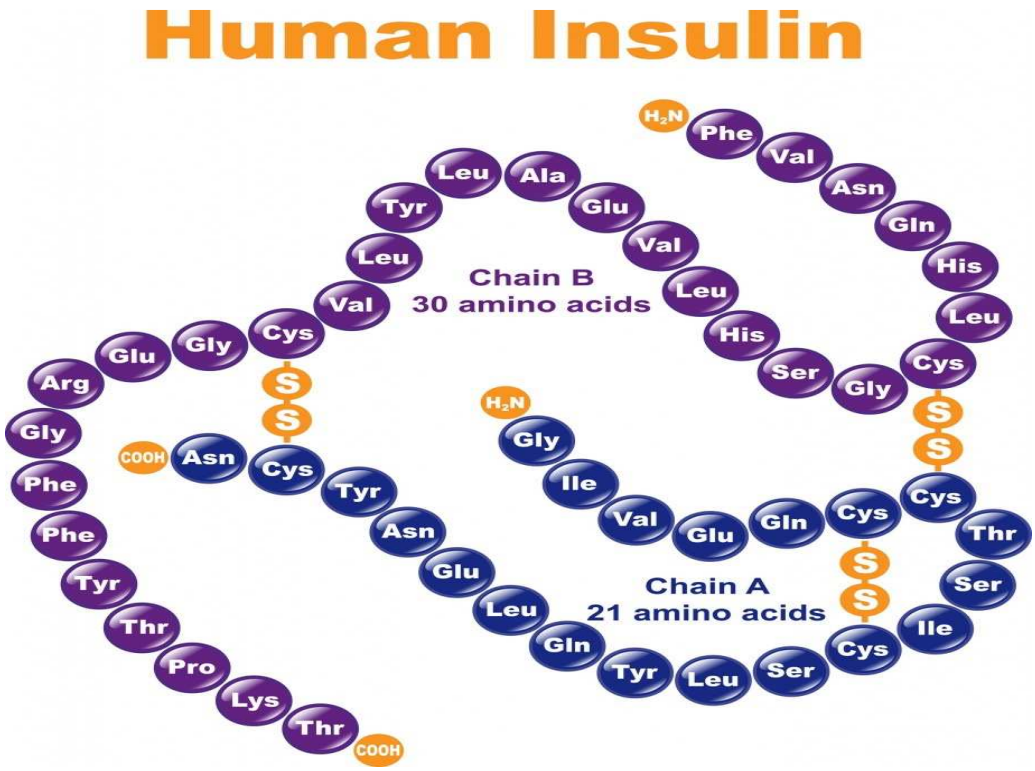


The endocrine part is made up of microscopic elements called Pancreatic islets of Langerhans. They are small islands of cells distributed throughout the gland. They appear most numerous in the tail. The islets have various types of cells of endocrine importance. Of the endocrine hormones secreted by the pancreas, Insulin and Glucagon play crucial role in the normalregulation of Glucose, Lipid and protein metabolism.

Endocrine Pancreatic Cells And Their Functions:

Cell type	Percentage of islet cells	Hormonal content
Beta	60–80	Insulin, IAPP/amylin (thyrotropin-releasing hormone, calcitonin gene–related peptide, gastrin, pancreastatin)
Alpha	15–20	Glucagon (glicentin, TRH, CCK, endorphin, glucagon-like polypeptide-1, peptide YY, DKP histidyl-proline diketopiperazine, pancreastatin)
Delta	5–10	Somatostatin (met-enkephalin, CGRP, pancreastatin)
PP	15–20	Pancreatic polypeptide (met-enkephalin, peptide YY)
δ_1	<1	Vasoactive intestinal polypeptide
EC	<1	Substance P, serotonin
G_1	<1	Gastrin (adrenocorticotropic hormone-related peptides)

INSULIN - CHEMISTRY AND SYNTHESIS:



It is a polypeptide hormone. Molecular weight - 5808 Da. The gene for encoding insulin INS gene, is located in the short arm of Chromosome 11, which has 3 exons and two introns.[19]

It has two chains connected by disulfide bonds. Porcine insuli differs from human insulin by one aminoacid.

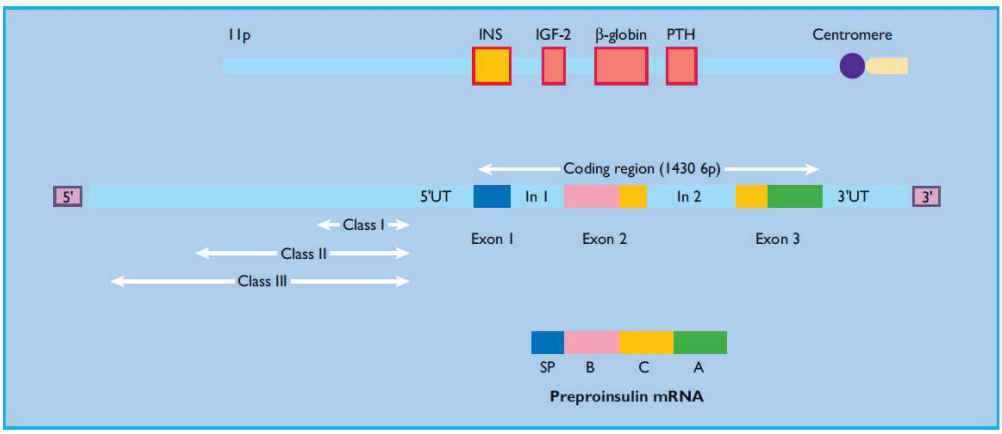


Figure 6.3 Structure of the human insulin gene. The coding region of the human insulin (INS) gene comprises three exons, which encode the signal peptide (SP), the B chain, C peptide and A chain. The exons are separated by two introns (In1 and In2). Beyond the 5′ untranslated region (5′UT), upstream of the coding sequence, lies a hypervariable region in which three alleles (classes I, II and III) can be distinguished by their size.

Preproinsulin is synthesized in endoplasmic reticulum of B cells. Molecular weight - 11,500 Da. It is transported to the Golgi apparatus.

The molecule is folded, disulfide bonds are formed to make Proinsulin. Molecular weight - 9000 Da.Two proteases are involved in this process. Proinsulin has no insulin activity.

The Connecting peptide (C peptide) permits folding and is detached before secretion from the granules.[20]

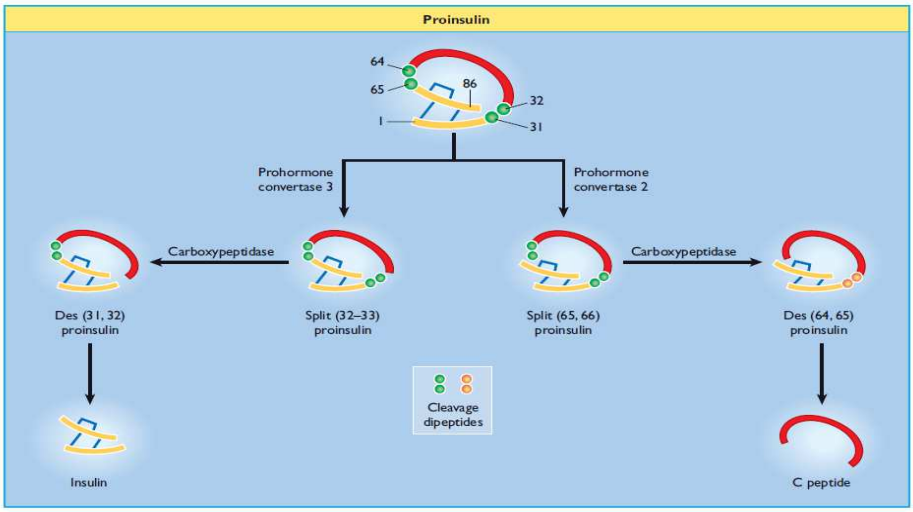


Figure 6.5 Insulin biosynthesis and processing. Proinsulin is cleaved on the C-terminal side of two dipeptides, namely Arg^{31}–Arg^{32} (by prohormone convertase 3) and Lys^{64}–Arg^{65} (prohormone convertase 2). The cleavage dipeptides are liberated, so yielding the "split" proinsulin products and ultimately insulin and C peptide.

It is packed into membrane bound granules here. The c-peptide is detached before release from the granules. Through microtubular transportation, the granules are transferred to the plasma membrane.

The contents of the granules are then expelled by exocytosis. 90-97% of the content expelled from the granules are insulin with an equimolar amount of c-peptide. Proinsulin forms the rest of the content.

Insulin has to cross the B cell basal lamina and the fenestrated endothelium of the neighbouring capillary.

The half life of insulin is very short. Its about 5 mins. Most of it binds to insulin receptors. The rest are internalized and degraded by protease namedinsulinase inside the endosomes. The degradation takes place mainly in the liver and to some extent in the muscles, kidneys and other tissues.

INSULIN RECEPTOR:

Insulin receptor has a molecular weight of about 3,40,000 kDa. It consists of 2 alpha subunits that is completely extracellular and 2 beta subunits which penetrate the membrane, extending into the cytoplasm.

The IGF - I receptor is very similar to insulin receptor, but the IGF - II receptor is not.

The beta subunits have Tyrosine kinase activity. Both subunits are held together by disulfide linkages. Insulin binds to the extracellular component and initiate the autophosphorylation of intracellular beta subunits.

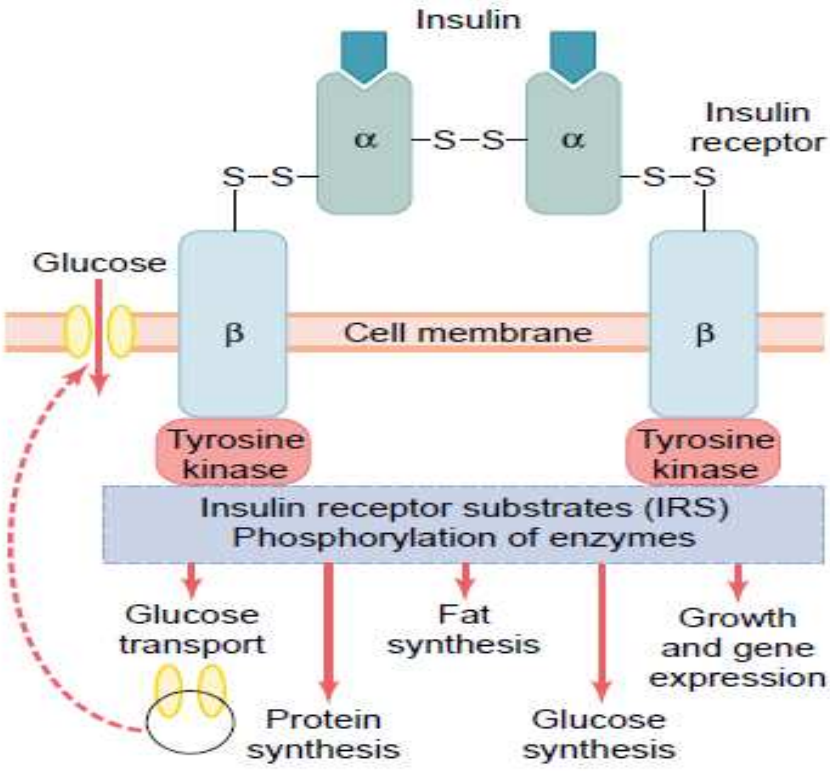


Figure 78–3

Schematic of the insulin receptor. Insulin binds to the α-subunit of its receptor, which causes autophosphorylation of the β-subunit receptor, which in turn induces tyrosine kinase activity. The receptor tyrosine kinase activity begins a cascade of cell phosphorylation that increases or decreases the activity of enzymes, including insulin receptor substrates, that mediate the effects of glucose on glucose, fat, and protein metabolism. For example, glucose transporters are moved to the cell membrane to facilitate glucose entry into the cell.

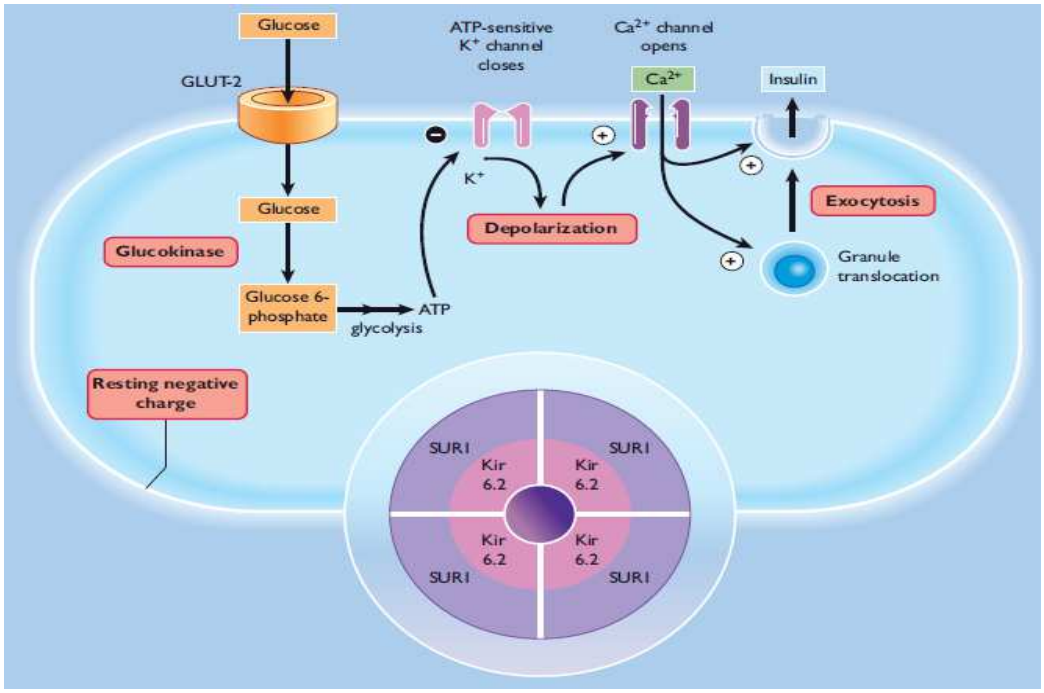
This in turn cause phosphorylation of many other enzymes located intracellularly.The half life of the receptor is 7 hours.

FACTORS AND CONDITIONS THAT INCREASE INSULIN SECRETION:[21]

- Increased blood glucose.
- Increased blood free fattyacids.
- Increased blood aminoacids.
- Gastrointestinal hormones: gastrin, cholecystokinin, secretin, gastric inhibitory peptide, glucagon like peptide - 1.
- Neurotransmitters: acetylcholine, vasoactive intestinal peptide, gastrin releasing polypeptide, Pituitary adenylate cyclase activating polypeptide
- Glucagon.
- Cortisol.
- Growth hormone.
- Beta adrenergic stimulation.
- Adiponectin.
- Insulin resistance.
- Adenine nucleotides.
- Divalent cations.

FACTORS AND CONDITIONS THAT DECREASE INSULIN SECRETION:

- Decreased blood glucose.
- Fasting.
- Somatostatin - 14, 28.
- Leptin.
- Ghrelin.
- Resistin.
- Galanin.
- Neuropeptide Y.
- Dopamine.
- Norepinephrine.
- Alpha adrenergic activation.



Intracellular mechanism by which glucose stimulates insulin release.

PRINCIPAL ACTIONS OF INSULIN:

Rapid (seconds):

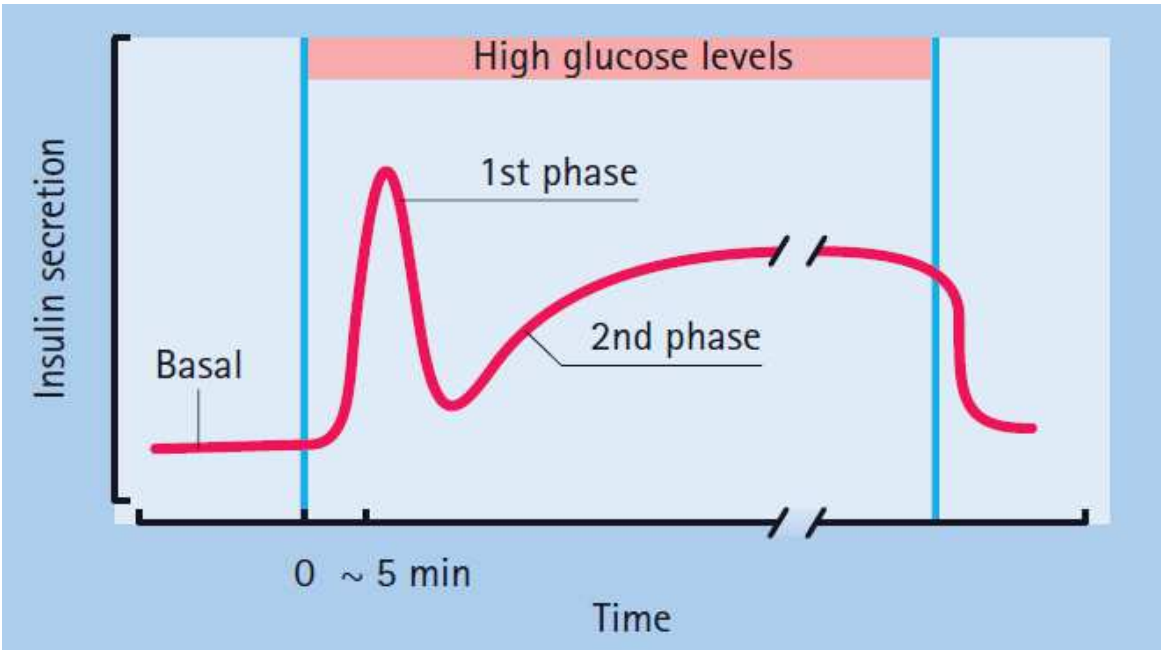
Increased transport of glucose, aminoacids and K+ into the insulin - sensitive cells.

Intermediate (minutes):

- Stimulation of protein synthesis.
- Inhibition of protein degradation.
- Activation of glycolytic enzymes and glycogen synthase.
- Inhibition of phosphorylase and gluconeogenic enzymes.

Delayed (hours):

Increase in mRNAs for lipogenic and other enzymes.



Insulin is secreted in two phases following the rise in glucose.

EFFECTS OF INSULIN ON VARIOUS TISSUES:[22]

General:

Increased cell growth.

Liver:

Decreased ketogenesis.

Decreased glucose output due to decreased gluconeogenesis, increased glycogen synthesis and increased glycolysis.

Increased protein synthesis.

Increased lipid synthesis.

Adipose tissue:

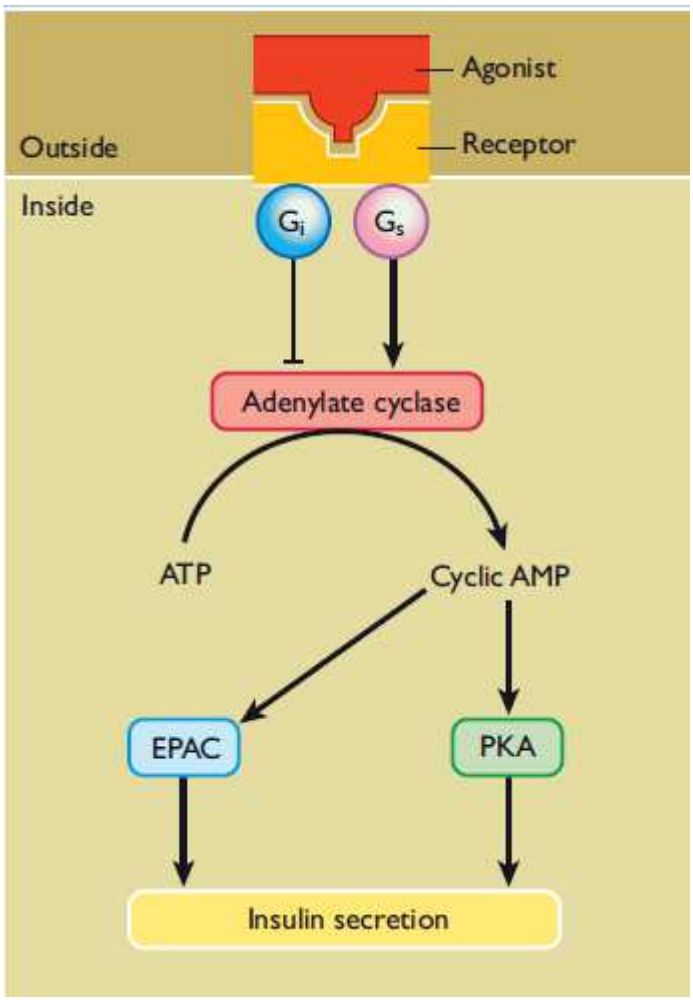
- Increased glucose entry.
- Activation of lipoprotein lipase.
- Inhibition of hormone sensitive lipase.
- Increased glycerol phosphate synthesis.
- Increased triglyceride deposition.
- Increased fatty acid synthesis.
- Increased K+ uptake.

Muscle:

- Increased glucose entry.
- Increased glycogen synthesis.
- Increased ketone uptake.
- Increased amino acid uptake.
- Increased protein synthesis in ribosomes.
- Decreased protein catabolism.
- Decreased release of gluconeogenic amino acids.
- Increased K+ uptake.

INTRACELLULAR REGULATION OF INSULIN SECRETION

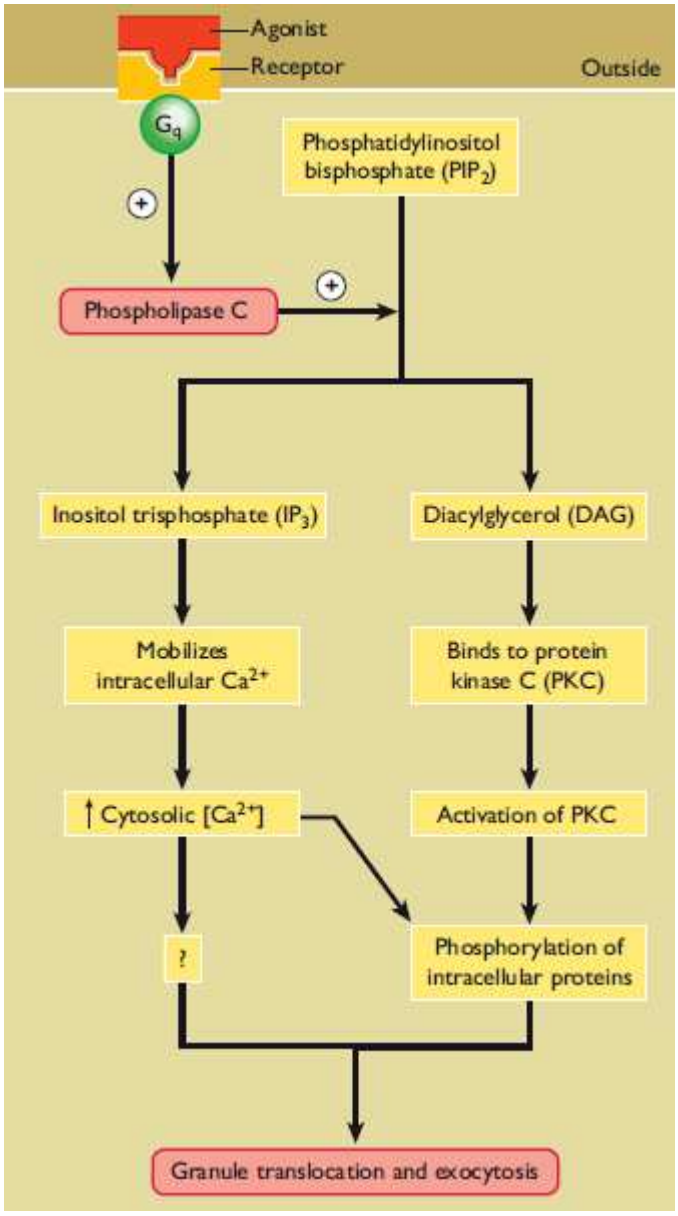
Insulin is inturn regulated by second messengers which are located intracellularly like Adenylate cyclase and Phospholipase C.



Intracellular regulation of insulin secretion by Adenylate cyclase

EPAC - Exchange proteins activated by cyclic AMP.

PKA - Protein kinase A.



Intracellular regulation of insulin secretion by Phospholipase C.

Phospholipase C hydrolyses Phosphoinositol bisphosphate to generate Inositol triphosphate and Diacyglycerol.

IP3 mobilises intracellular calcium from endoplasmic reticulum.

DAG activates protein kinase C. Both facilitate insulin release.

PATHOGENESIS OF DIABETES MELLITUS:

DIABETES MELLITUS TYPE 1:

The pathogenesis behind the development of Diabetes Mellitus type - 1 is autoimmune destruction of the isletic pancreatic beta cells. Although it manifests itself abruptly in young individuals, the process is a chronic one. 90% of the beta cells are destroyed before the clinical manifestation occurs. Several mechanisms are found to cause the destruction of the beta cells.

Interaction of T-cells with the B-cell antigen causes major damage to the beta cells. TH1 subset of CD4+ cells mediate macrophage activation and resultant cell destruction. Cytotoxic T cells of CD8+ type attack the beta cells directly and also through activating macrophages by the secreted cytokines. In a group of people of diabetes mellitus type 1 disease, autopsy of the pancreas showed inflammatory infiltrate contatining CD4+ and CD8+ cells. Cellular necrosis was found and the lesion were called insulinitis. The major cytokines responsible for the destruction of the beta cells are Interferon gamma, Tumour necrosis factoralpha and Interleukin - 1.

Many mouse model experiments implied the antigenic target as Insulin Glutamic acid dehydroxylase (GAD), ICA-512/IA-2 and a beta cell specific zinc transporter (ZnT-8).

Genetic considerations:

There is 40 - 60% concordance between identical twins. HLA DQA1*03001, DQB1*0302, DQB1*0201 have been found to strongly associated than any othey haplotype. They are present in 40% of children. The gene that is strongly associated with DM type 1 is located in chromosome 6 corresponding to HLA region which encodes Major Histocompatibility Complex Class II. Atleast 20 loci have been mapped for the genetic predisposition.

Polymorphisms in the insulin gene promoter region, interleukin Receptor, CTLA-4 gene, PTPN22, CTLA4 are some of them. HLA DQA1*0102, HLA DQB1*0602 offer protection against the Disease and are extremely rare. Relatives have a 10 fold high chance of getting the disease.

Environmental factors:

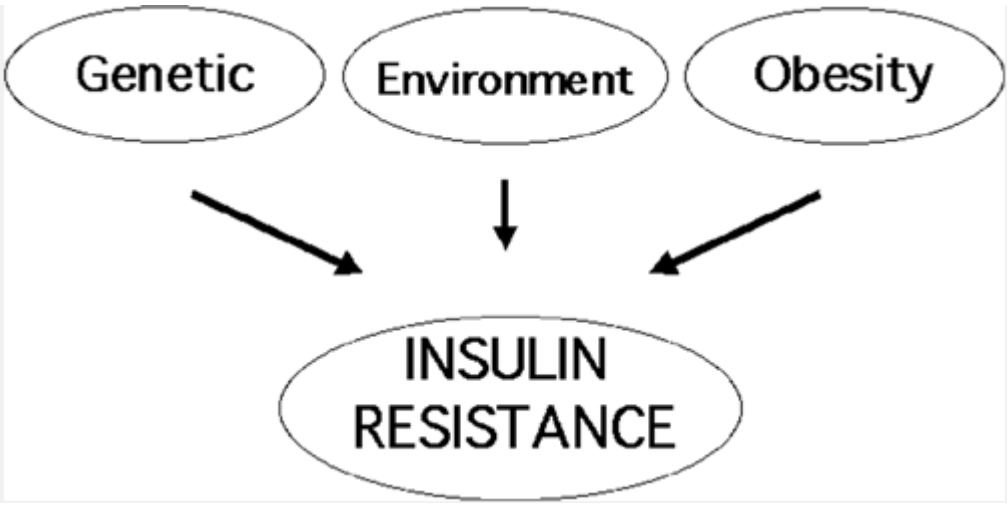
Bovine milk proteins.

Nitrosourea compounds.

Coxsackie, Rubella and Enteroviruses.

DIABETES MELLITUS TYPE 2:[23]

Its pathogenesis revolves around Insulin Resistance and Abnormal Insulin Secretion. Multiple studies reveal that insulin resistance is The forerunner of insulin secretory defect, but for diabetes to develop, insulin secretion should become deficient. East Asians and South Asians have predominantly dysfunction of beta cells, while Latin Americans have insulin resistance as the main pathology. DM T2 is charecterised by abnormal fat metabolism, insulin resistance, decreased insulin secretion and excessive hepatic glucose production.



Insulin resistance:

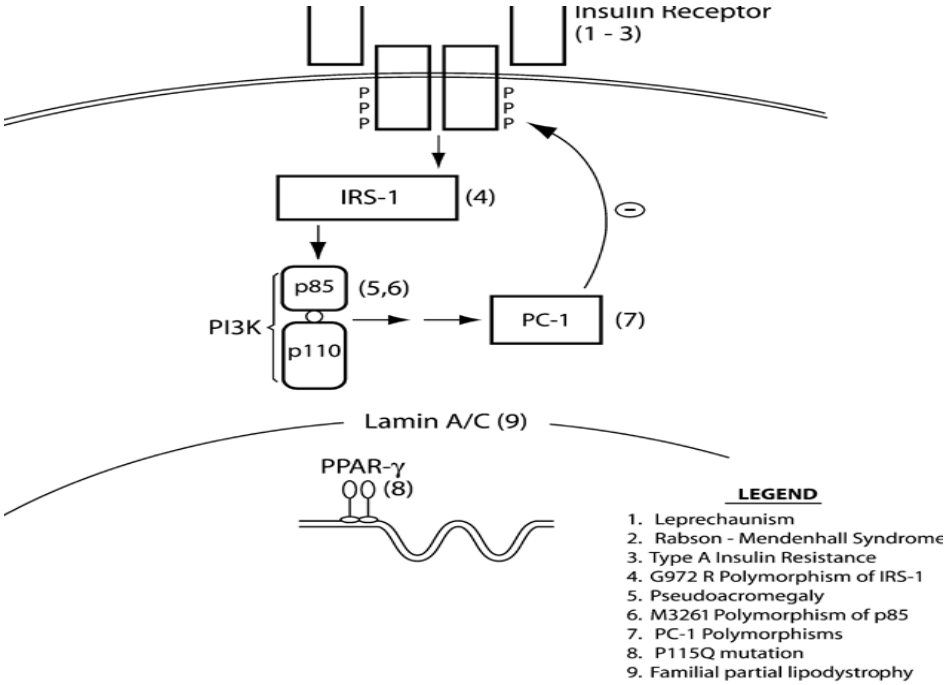
It is charecterised by

i)Decrease in tyrosine kinase activity of insulin receptor.

ii)Decrease in insulin receptors.

The defects in postreceptor insulin regulated dephosphorylation / phosphorylation play an important role for the development of insulin resistance. It is also caused by some adipokines and increased production of free fattyacids.

Skeletal muscles are affected before the liver. In skeletal muscles uptake of 3 -O- methylglucose which is stimulated by insulin is significantly low compared to normal individuals.[24-25] There is significant decrease in second messenger activity mediated by Insulin Receptor Substrate - 1 (IRS-1). Proximal insulin signaling is downregulated. Plasma cell differentiation factor - 1 (PC-1) is an intrinsic inhibitor of insulin receptor tyrosine kinase activity. It is a glycoprotein with ectonucleotide pyrophosphate activity. Muscle expression of PC - 1 has negative correlation for insulin sensitivity.[26] There is a strong association between PC-1 expression for insulin receptor downregulation than with decreased expression of insulin receptor Protein-tyrosine phosphatase-1B has negative downregulative action on the phosphorylation of insulin receptor and IRS-1.[27-28]There is positive association between insulin resistance andhepatic accumulation of fat.



Insulin resistance syndrome/Metabolic syndrome is a symptomatic constellation including insulin resistance, dyslipidemia, DM T2 or IGT/IFG, accelerated cardiovascular disease, hypertension, central or visceral obesity. There is increased expression of Peroxisome Proliferator Activated Receptor Gamma.

Many medical conditions are associated with insulin resistance. Systemic lupus erythematosus, Renal failure, Uremia, Cirrhosis of liver, Hemochromatosis, Thalassemia in association with transfusion induced iron overload, Gastrointestinal malignancies are a few of them.

The inhibitory effects of chronic hyperglycemia on action and secretion of insulin has been termed as Glucose Toxicity. Insulin

resistance induced by hyperglycemia includes a defect in insulin - stimulated glycogen synthesis and downregulation of the glucose transport system by hyperglycemia.

Development of insulin resistance:

First phase : Normal plasma glucose despite demonstrable insulin resistance, because of high insulin levels.

Second phase : Worsening of insulin resistance leading to post prandial hyperglycemia despite of high insulin secretion.

Third phase : There is no change in the level of insulin resistance but fasting hyperglycemia occurs because of declining insulin sectretion.

Insulin resistance syndromes:[29-30]

Type A - young women, obesity, severe hyperinsulinemia and features of hyperandrogenism. Undefined defect in the pathway of insulin – signaling.[31]

Type B - middle - aged women, severe hyperinsulinemia, features of hyperandrogenism and autoimmune disorders. Autoimmune antibodies against insulin receptor. Auto – stimulation of the receptor leads to intermittent hypoglycemia.

METABOLIC SYNDROME:

The New International Diabetes Federation defines metabolic syndrome as Central obesity + two of the four factors.[32]

Hypertriglyceridemia : ≥ 150 mg/dl or specific medication.

Low LDL cholesterol : < 40 mg/dl for men and < 50 mg/dl for women.

Hypertension (BP): ≥ 130 mmHg (systolic) or

≥85 mmHg (diastolic) or specific medication.

Fasting Plasma Glucose : ≥ 100 mg/dl or specific medication or previously diagnosed Type 2 Diabetes.

Central obesity is defined as waist circumference > 90 cm for South Asian males and > 80 cm for South Asian females.

Impaired insulin secretion:

Initially the first phase is affected that is insulin secretion in response to glucose. Later non glucose secretagogues mediated insulin secretion is also affected. In contrast to 90% reduction in beta cell function present in Type 1 DM, Type 2 DM is charecterised by 50% reduction. Fibrillar amyloid depositon following amylin secretion may contribute to beta cell dysfunction.

Genetic considerations:

In contrast to type 1 disease type 2 has 70-90% concordance Between identical twins. There is 40% chance for the child to get the disease if both of its parents are affected. More than 70 genes are identified, of which the most prominent is a Transcription Factor 7-like 2 gene variant. Genes encoding the proteins peroxisome proliferator - activated receptor gamma, zinc transporter, IRS, calpain 10, inward rectifying potassium channel show genetic polymorphisms.

MONOGENIC FORMS OF DIABETES MELLITUS:[33]

Mode of inheritance is Autosomal Dominant.

Maturity onset diabetes of young (MODY) is associated with mutation in the specific genes.

MODY 1 - Hepatocyte nuclear transcription factor (HNF) 4 alpha.

MODY 2 - Glucokinase.

MODY 3 - HNF 1 alpha.

MODY 4 - Insulin promoter factor (IPF) 1.

MODY 5 - HNF 1 beta.

MODY 6 - NeuroD1.

Transient of Permanent Neonatal Diabetes - ATP sensitive

Potassium channel subunits (Kir6.2 and ABCC8) and Insulin gene.

RISK FACTORS FOR DEVELOPMENT OF TYPE 2 DIABETES MELLITUS

Family history of diabetes.

Obesity.

Physical inactivity.

Race/ethnicity.

Previously identified with impaired fasting glucose, impaired glucose tolerance, or a HbA1c of 5.7 - 6.4%.

History of GDM or delivery of baby > 4kg.

Hypertension.

Polycystic ovarian syndrome or acanthosis nigricans.

History of cardiovascular disease.

HDL cholesterol < 35 mg/dl and/or a Triglyceride > 250 mg/dl.

CRITERIA FOR DIAGNOSIS OF DIABETES MELLITUS[34]

1) Symptoms of diabetes + random blood glucose* $\geq$ 200 mg/dl.
2) Fasting plasma glucose** $\geq$ 126 mg/dl.
3) Hemoglobin A1c $\geq$ 6.5%.

4) 2 - hour plasma glucose $\geq$ 200 mg/dl using an oral glucose tolerance test***.

*Random is defined as without regard to the time since last meal.

**Fasting is defined as no calorie intake for a time period of atleast 8 hours.

***The test should be performed using a glucose load containing the equivalent of 75 gram anhydrous glucose dissolved in water. Not recommended for routine clinical use.

TREATMENT OF DIABETES MELLITUS

GOAL:[35]

Eliminate symptoms of hyperglycemia.

Allow the patient to have a normal lifestyle as much as possible.

Eliminate or reduce longterm macro and microvascular Complications.

INDEX	GOAL
HbA1c	< 7.0%
Preprandial capillary plasma glucose	80 - 130 mg/dl
Peak postprandial capillary plasma glucose	< 180 mg/dl
Blood pressure	< 140/90 mg/dl
Low - density lipoprotein	< 100 mg/dl
High - density lipoprotein	> 4o mg/dl in men > 50 mg/dl in women
Triglycerides	< 150 mg/dl

SYMPTOMS:

Thirst, dry mouth.

Polyuria.

Nocturia.

Change in weight (usually loss of weight)

Lethargy, fatigue.

Blurring of vision.

Balanitis, pruritus vulvae.

Headache.

Nausea.

Hyperphagia with predilection for sweet foods.

Mood change, apathy, irritability, difficulty in concentration.

TREATMENT

Type 1 Diabetes Mellitus :

Insulin therapy to replace the deficient insulin.

Type 2 Diabetes Mellitus :

Adequate glycemic control can be achieved by :

Lifestyle and diet control in 50%.

Oral Hypoglycemic Agents in 20 - 30%.

Insulin therapy in 20 - 30%.

Regular physical activity, Healthy diet, Avoidance of stress forms the first step in the treatment of type 2 diabetes.

Aim of dietary management:[36]

Good glycemic control:

Avoid hypoglycemia and reduce hyperglycemia.

Assist with weight management.

Weight loss for obese and overweight individuals.

Ensure adequate nutritional intake.

Reduce the risk of macro and microvascular complications.

Avoid atherogenic diets.

Avoid diets that aggravate complications, for example high

protein intake in nephropathy.

Recommended % of energy intake:

Carbohydrate : 45-60%.

Sucrose : upto 10%.

Fat (total) : < 35%.

Omega - 6 polyunsaturated : < 10%

Omega - 3 polyunsaturated : 140 gram of oily fish once or twice weekly.

Monounsaturated : 10 - 20%.

Saturated : < 10%.

Protein : 10 - 15%. Not to exceed

1g/kg body weight/day.

Fruits/Vegetables : 5 portions daily.

ORAL HYPOGLYCEMIC AGENTS :

	Mechanism of Action	Examples[a]	HbA_{1c} Reduction (%)[b]
Oral			
Biguanides[c*]	↓ Hepatic glucose production	Metformin	1–2
α-Glucosidase inhibitors[c**]	↓ GI glucose absorption	Acarbose, miglitol, voglibose	0.5–0.8
Dipeptidyl peptidase IV inhibitors[c***]	Prolong endogenous GLP-1 action	Alogliptin, Anagliptin, Gemigliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin, vildagliptin	0.5–0.8
Insulin secretagogues: Sulfonylureas[c*]	↑ Insulin secretion	Glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glyburide, glyclopyramide	1–2
Insulin secretagogues: Nonsulfonylureas[c***]	↑ Insulin secretion	Nateglinide, repaglinide, mitiglinide	0.5–1.0

Maximum HbA1c reduction is done by Sulfonylureas and Biguanides.

Sodium-glucose co-transporter 2 inhibitors[c,***]	↑ Urinary glucose excretion	Canagliflozin, dapagliflozin, empagliflozin	0.5–1.0
Thiazolidinediones[c,***]	↓ Insulin resistance, ↑ glucose utilization	Rosiglitazone, pioglitazone	0.5–1.4
Parenteral			
Amylin agonists[c,d,***]	Slow gastric emptying, ↓ glucagon	Pramlintide	0.25–0.5
GLP-1 receptor agonists[c,***]	↑ Insulin, ↓ glucagon, slow gastric emptying, satiety	Exenatide, liraglutide, dulaglutide	0.5–1.0
Insulin[c,d,****]	↑ Glucose utilization, ↓ hepatic glucose production, and other anabolic actions	See text and Table 418-4	Not limited
Medical nutrition therapy and physical activity[c,*]	↓ Insulin resistance, ↑ insulin secretion	Low-calorie, low-fat diet, exercise	1–3

Regular physical activity and Medical nutrition therapy provide greater HbA1c reduction compared with other oral hypoglycemic agents.

Regular assessment of glycemic control is essential to prevent shorterm and longterm complications.

Biochemical tests used for monitoring are as follows:

Present state of diabetes control – Blood glucose monitoring.

Retrospective assessment :

Immediate past(few hours) - Urine glucose testing.

Recents past (few weeks) - Fructosamine, Glycosylated albumin.

Remote past (few months) - Glycosylated hemoglobin.

Relation between HbA1c and mean plasma glucose in Standardized assays:

HbA1c	Mean plasma glucose (mg/dl)
6%	126
7%	154
8%	183
9%	212
10%	240
11%	269
12%	298

Self Monitoring of Blood Glucose is recommended in:

1) Patients on multiple doses of insulin therapy.
2) Pregnancy.
3) Patients prone to recurrent hypoglycemia.
4) During acute illness and in peri-operative period.

Glycated Hemoglobin (HbA1c):

Glycated Hemoglobin (HbA1c) measurement is the standard method to assess the long term control of diabetes. Non - enzymatic glycation of hemoglobin is increased when plasma glucose is consistently elevated. The half life of erythrocytes is 120 days. HbA1c thus reflects the glycemic history over the past 2-3 months. Out of this value 50% is contributed by the previous months glycemic level.

EMERGENCIES IS DIABETES MELLITUS:

Diabetic ketoacidosis,

Hyperglycemic hyperosmolar state.

Hypoglycemia.

DIABETES RELATED COMPLICATIONS:[37]

Macrovascular:

Coronary heart disease.

Cerebrovascular disease.

Peripheral arterial disease.

Microvascular:

Neuropathy

Autonomic.

Sensory and motor.

Nephropathy (albuminuria and falling renal function).

Ocular

Macular edema.

Retinopathy.

Other:

Gastrointestinal

Gastroparesis.

Diarrhea.

Genitourinary

Uropathy.

Sexual dysfunction.

Dermatologic.

Infectious.

Cataracts.

Glaucoma.

Hearing loss.

Cheiroarthropathy.

Periodontal disease.

Uncertain relationship to hyperglycemia

Depression.

Obstructive sleep apnea.

Fatty liver disease.

Hip fracture.

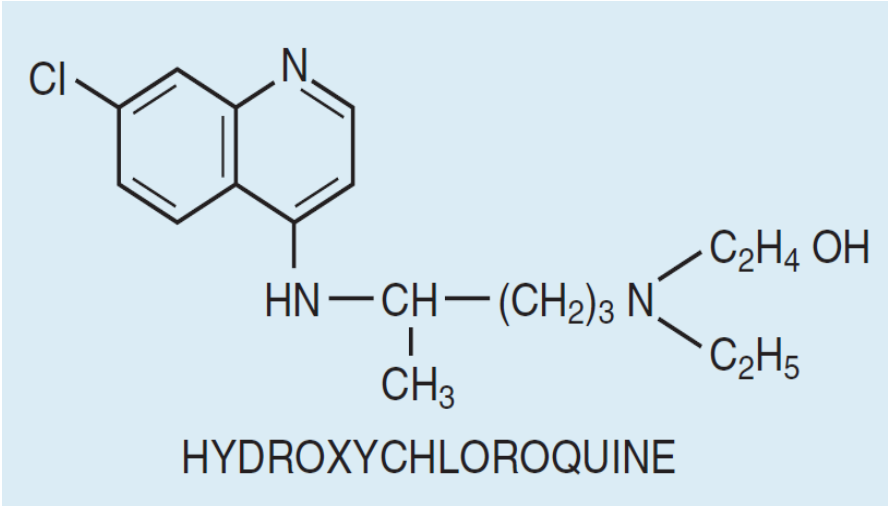
Osteoporosis (in type 1 diabetes mellitus).

Cognitive impairment or dementia.

Low testosterone in men.

HYDROXYCHLOROQUINE

Hydroxychloroquine and its progenor Chloroquine are nonbiologic drugs used mainly in the treatment of malaria and in rheumatic diseases. It is a well tolerated Disease Modifying Anti Rheumatic Drug. It belongs to aminoquinolone group of drugs. The first drug used from this group was quinine, but due to its toxicity chloroquine and hydroxychloroquine were developed.



HYDROXYCHLOROQUINE

Hydroxychloroquine differs from chloroquine by a hydroxyethyl group instead of an ethyl group on the tertiary amino nitrogen of the chloroquine sidechain.[38]

MECHANISM OF ACTION:

It is a weak base and hence can pass through cytoplasmic membrane inside the cytoplasmic vesicles and accumulate there. It increases the intravesicular pH to 6.0 from 4.0 thus interfering with the acid dependent subcellular functions.

This increased pH is noted to have many postulated immunoregulatory effects including attenuation of antigen processing and its presentation; stabilization of lysosomal membranes; inhibition of cell-mediated cytotoxicity.[39-40]

Receptor assembly gets disrupted including the Major Histocompatibility Complex class II molecules, since the high pH in the endoplasmic reticulum stabilises the MHC protein and prevents its displacement by low affinity autoantigens.[41]

Together with the decreased membrane receptor recycling there is downregulation of antigen presentation.[42]

It has an overall inhibitory effect on proinflammatory cytokines. Hydroxychloroquine has been observed to block

Interleukin - 1, Interleukin - 6, Interferon gamma production by monocytes.[43-44]

It has antioxidant properties and hence protects the tissue against damage by free radicals.[45]

It inhibits platelet aggregation and adhesion, leading to ananti-thrombotic effect.[46-47]

It favours lipid profile by reducing the triglycerides, low density lipoproteins, total cholesterol and very low densitylipoproteins in particular patients on corticosteroid therapy concomitantly.[48]

The half-life of hydroxychloroquine is 40 to 50 days and the plasma levels will start to increase gradually and equilibrate in 3 to 4 months.[49]

Most of the drug is excreted unchanged in urine. A part of the drug is metabolized to a desethyl derivative. Rest of the drug is excreted in the faeces.[50]

NOVEL EFFECTS FAVOURING ITS USE IN DIABETES:

The first described antidiabetic effect of Chloroquine was in the year 1984, in a diabetic patient with severe insulin resistance in whom after adding Chloroquine insulin requirement decreased drastically.[51]

Hydroxychloroquine decreases the plasma glucose levels by the inhibition of insulin degradation inside the golgi apparatus.[52-53] Animal models have demonstrated an inhibitory effect exerted by Hydroxychloroquine on insulin metabolism, including reduction in intracellular insulin degradation and an increase in intracellular insulin accumulation, slowing of insulin receptor recycling and stimulation of insulin mediated glucose transport.[60]

There is a potential ability for Hydroxychloroquine to decrease HbA1c in diabetic patients and coexisting Systemic Inflammatory Disease.[54] There is reduced risk of incident diabetes in Rheumatoid Arthritis patients even after glucocorticoid use and control of disease activity.[55]

Hydroxychloroquine has been shown to improve peripheral insulin sensitivity and insulin secretion in invitro and animal studies.

Inflammation has been considered to play a very important inter- mediary role in the pathogenesis of a number of co-existing diseases including diabetes. Interleukin - 6 and C - reactive protein are the two sensitive physiological markers of associated insulin resistance, hyperglycemia, overt diabetes mellitus and sub-clinical inflammation. Hydroxychloroquine exerts anti-diabetic effect by anti-

inflammatory action by inhibiting interleukin - 6 and C – reactive protein production.[56]

Adding Hydroxychloroquine to either Glibenclamide or Insulin in treating refractory noninsulin dependent has resulted in a fall in HbA1c by 3.3% over 6 months and 30% less insulin dose.[57]

Similar effects were observed in Sulfonylurea refractory Diabetes Mellitus Type 2 patients treated with Hydroxychloroquine, where HbA1c reduction was reported as 1.02.[58]

In patients with diabetes and coexisting rheumatoid arthritis and treated with Hydroxychloroquine0.66% reduction in HbA1c levels is reported.[59]

INDICATIONS FOR USE:

- Rheumatoid arthritis.
- Systemic Lupus Erythematosus.
- Discoid Lupus.
- Sjogren's Syndrome.
- Antiphospholipid Syndrome.

Miscellaneous:

- Palindromic rheumatism.
- Childhood dermatomyositis.
- Eosinophilic fasciitis.

- Erosive arthritis.
- Childhood systemic lupus erythematosus.

DOSAGE:

- 200 mg twice - thrice daily.
- Maintained at a dose of 6.5 mg/kg/day or less.

TOXICITY:

Ocular :

- Retinopathy (Bull's eye maculopathy):
- risk factors : high dosage (>6.4 mg/kg/day),
- longer duration of use (>5 yrs), liver or kidney
- disease, age >60 yrs.
- Corneal opacity.

Dermatologic :

- Rash.
- Photosensitivity.
- Alopecia.
- Depigmentation of hair.

Neuromuscular:

Headache.

Tinnitus and deafness.

Irritability, insomnia and nightmares.

Neuromyotoxicity - Proximal muscle weakness, cardiac myotoxicity

Peripheral neuropathy.

Cardiovascular:

Conduction defects and cardiomyopathy.

Gastrointestinal:

Nausea, vomiting, abdominal cramps and diarrhea.

Pregnancy, fertility and lactation:

Category C, no teratogenic effects reported, in breast milk low concentration is secreted.

Hydroxychloroquine accumulates is melanin containing cells like Skin and Retinal pigment epithelium and hence the toxicity.

Toxicity monitoring:

After 5-7 years of use there is 1% risk of retinal toxicity.

Similar effect is observed following a cumulative dose of 1000 gram.

Annual eye examination should be done from 5 years of treatment initiation.

Contraindication:

Previous visual field or retinal changes related to 4-aminoquinoline agents or hypersensitivity to it.

Severe liver disease due to viral hepatitis.

RHEUMATOID ARTHRITIS

A chronic, inflammatory disease of unknown aetiology charecterised by symmetric, peripheral arthritis. The hallmark pathology are synovial inflammation and proliferation, thinning of articular cartilage and focal bone erosions. It is treated with Non steroid anti-inflammatory drugs, Disease Modifying Anti Rheumatic Drugs, Glucocorticoids, Anti – Tumor Necrosis Factor Agents, and Biologicals. Hydroxychloroquine is used for its anti –inflammatory and immunomodulatory action.

SYSTEMIC LUPUS ERYTHEMATOSUS

It is a autoimmune disease. Cell and organ get damaged initially which is mediated by immune complexes and tissue binding auto antibodies. It affects almost all organs. Treatment is with NSAIDS, Cyclophosphamide, Mycophenolate mofetil, Hydroxychloroquine, Biologics, and Glucocorticoids.

MATERIALS

AND

METHODS

MATERIALS AND METHODS

The study was conducted at the Department of Rheumatology, Madras Medical College and Rajiv GandhiGovernment General Hospital, Chennai -600003.

ETHICAL COMMITTEE APPROVAL:

Obtained.

PATIENT CONSENT:

Obtained.

DURATION OF THE STUDY:

6 months.

STUDY DESIGN:

Observational study.

SAMPLE SIZE:

100 patients.

INCLUSION CRITERIA:

1. Patients above 16 years of age.

2. Patients with rheumatological disease.

3. Patients receiving hydroxychloroquine.

4. Patients receiving similar drugs in the same dosage.

EXCLUSION CRITERIA:

1. Paediatric patients.
2. Pregnant females.
3. Antenatal mothers.
4. Diabetic Ketoacidosis.
5. Critically ill patients.
6. Hematological disorders.
7. Any change in medications or their dose during the study period.

SELECTION OF PATIENTS:

Patients attending rheumatology outpatient department with newly diagnosed rheumatological disease are selected based on the inclusion and exclusion criteria.

DATA COLLECTION AND METHODS:

Patients satisfying the inclusion and exclusion criteria are selected. Blood samples are collected. Complete blood count, Renal function test and Liver function test are done. Before initiating Tablet Hydroxychloroquineat a dose of 200 mg twice daily, for the

treatment of their rheumatologicalillness, baseline HbA1c, Fasting bloodsugar, Postprandial blood sugar are measured. Based on the results, patients are grouped into one of the three groups namely, Diabetes Mellitus, Impaired Glucose Tolerance and Normal glucose Tolerance as defined by American Diabetes Association.

Patients are followed up after 3 months.The same investigations are repeated. The results obtained after3 months of treatment with Hydroxychloroquine are compared with the baselinevalues. The results are subjected to statistical analysis.

STATISTICAL ANALYSIS:

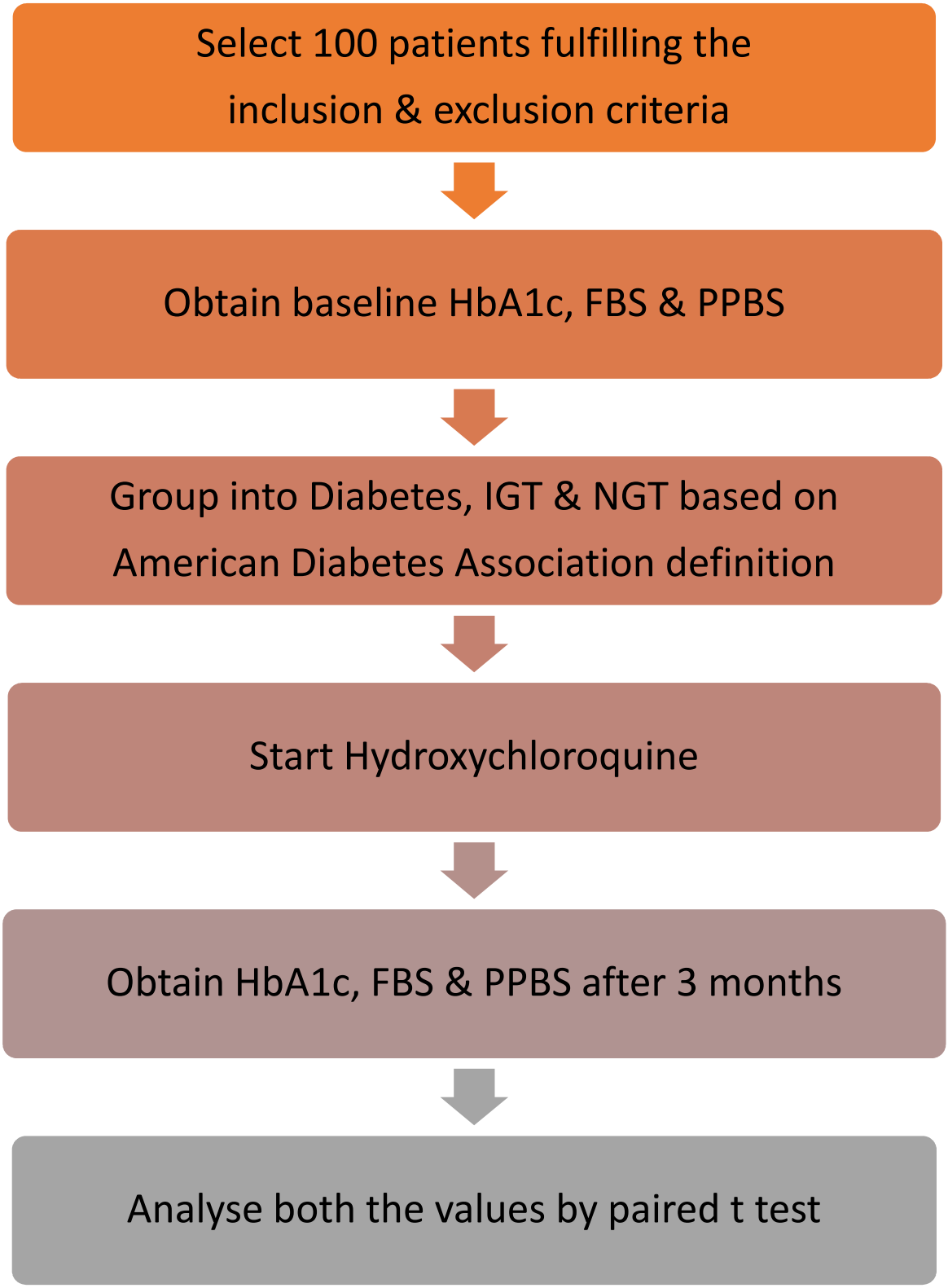
The results are analysed using SPSS software version 21. Association between the two variables was analysed using paired-sample t test.The primary efficacy measures were the mean change in HbA1c, Fasting blood sugar and Postprandial blood sugar from the baseline to 3 months.Statistical significance is assumed with a p value of 0.05.

SPONSORSHIP:

No

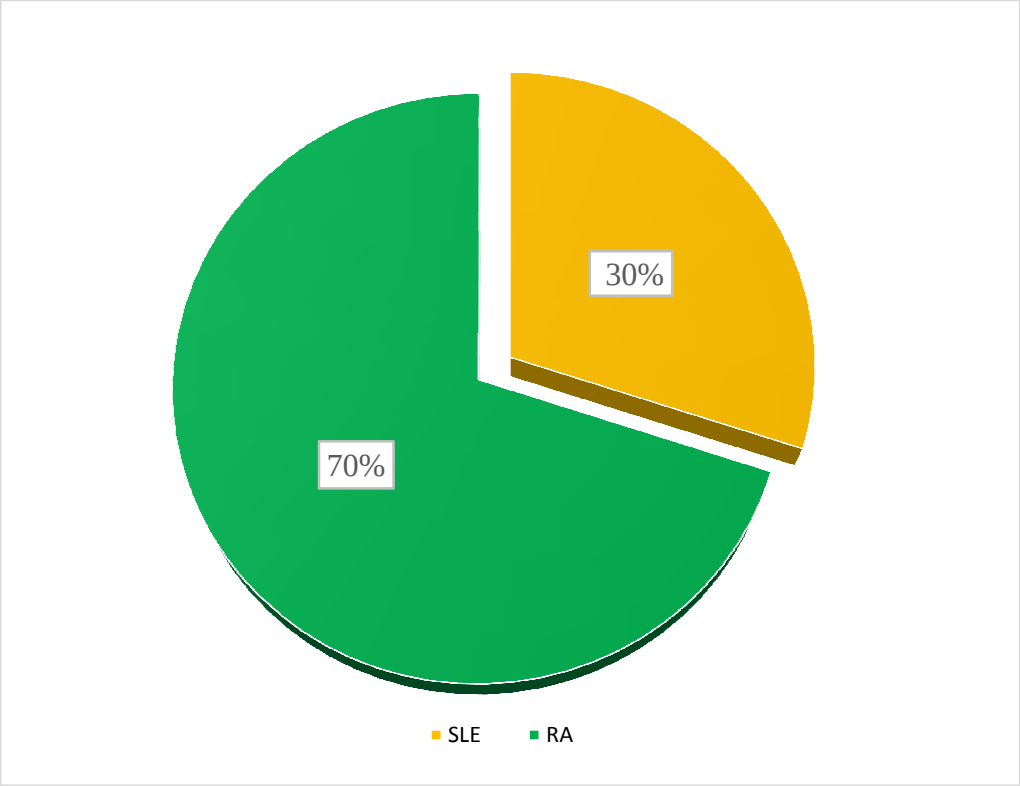
CONFLIT OF INTEREST

None


Select 100 patients fulfilling the inclusion & exclusion criteria
Obtain baseline HbA1c, FBS & PPBS
Group into Diabetes, IGT & NGT based on American Diabetes Association definition
Start Hydroxychloroquine
Obtain HbA1c, FBS & PPBS after 3 months
Analyse both the values by paired t test

OBSERVATION AND RESULTS

DISEASE DISTRIBUTION



SLE - Systemic Lupus Erythematosus

RA - Rheumatoid Arthritis

OBSERVATION

AND

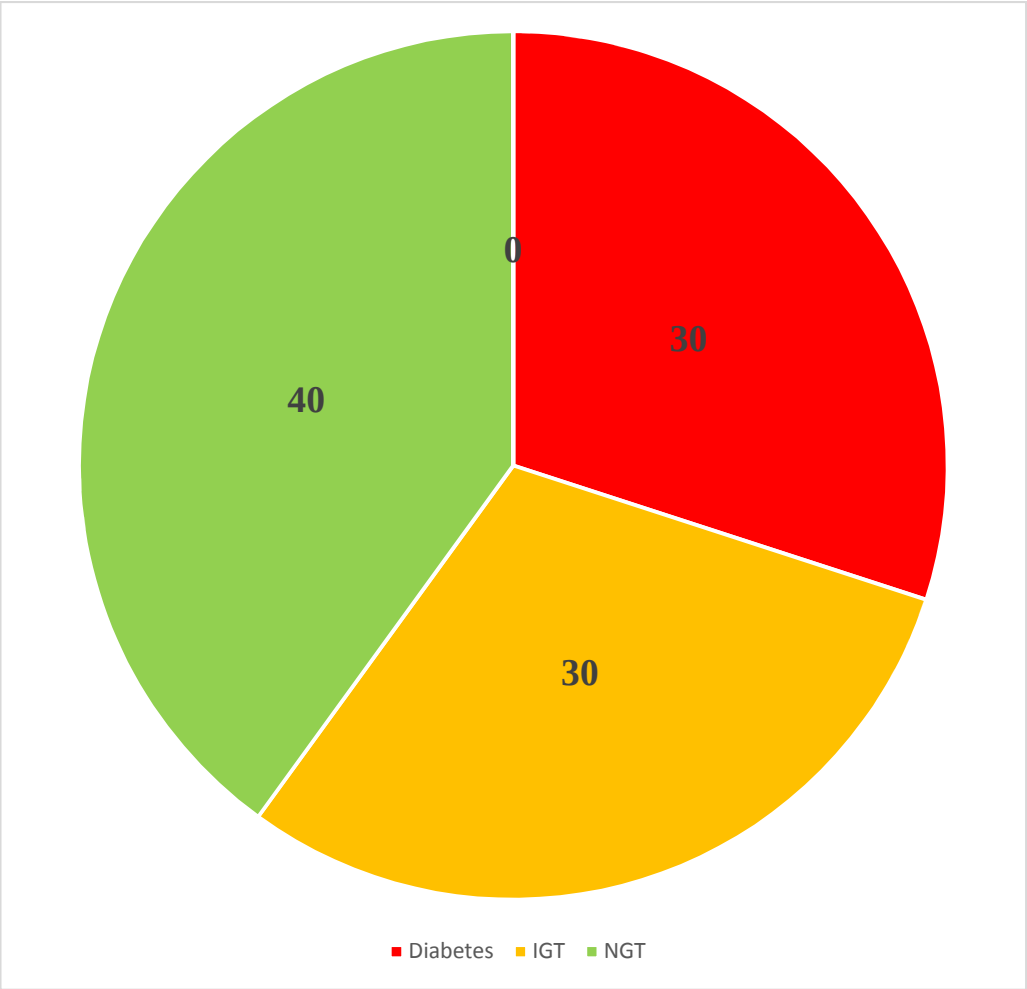
RESULTS

DISEASE DISTRIBUTION

	SLE	RA
Number of Patients	30	70

In our study group, majority of patients had Rheumatoid Arthritis, constituting 70% of the study population.

PREVALENCE OF DIABETES, IGT AND NGT IN THE STUDY GROUP



IGT - Impaired Glycemic Tolerance

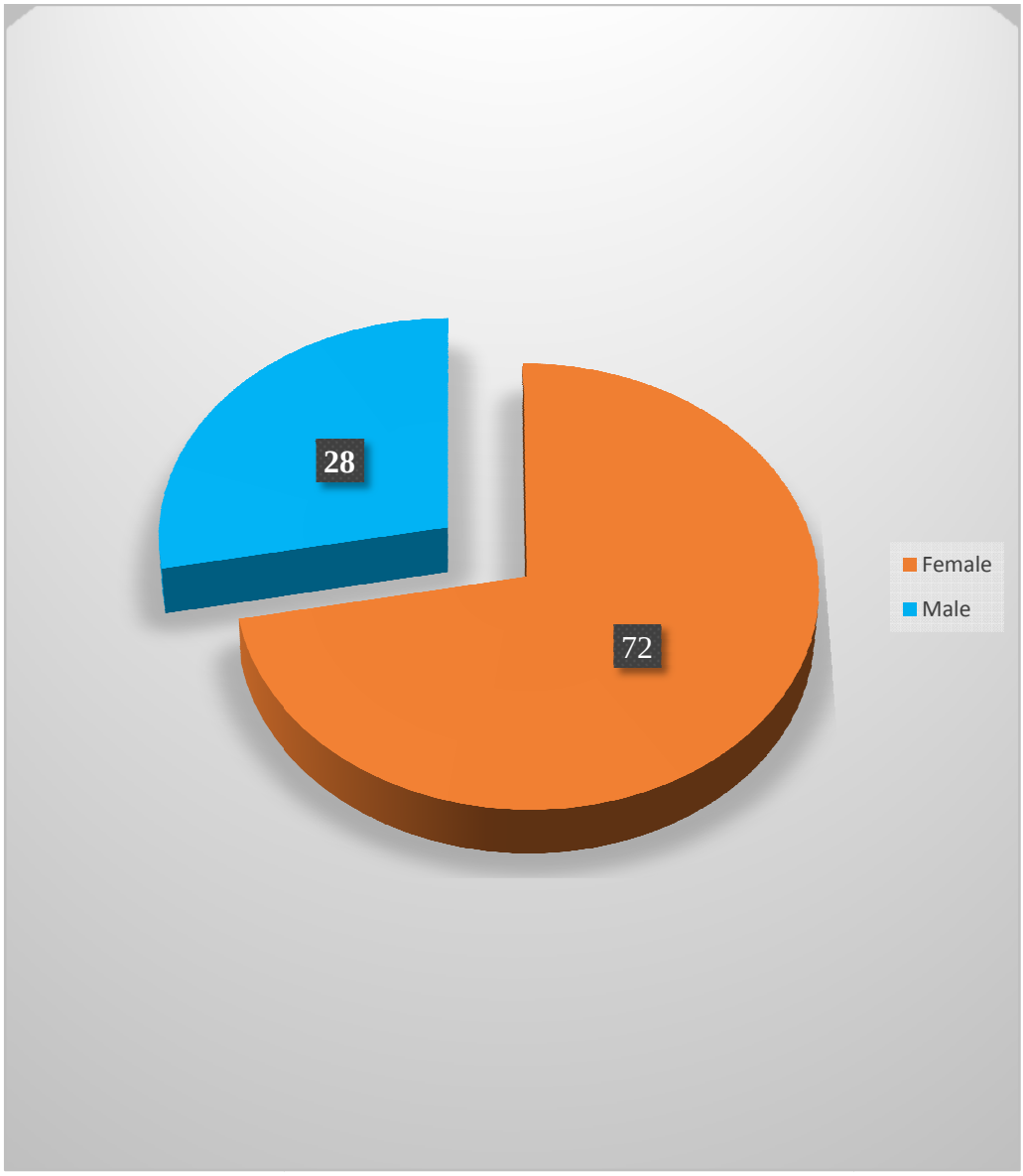
NGT - Normal Glycemic Tolerance

PREVALENCE OF DIABETES, IGT AND NGT IN THE STUDY GROUP

Glycemic Status	Diabetes	IGT	NGT	Total
Number of Patients	30	30	40	100

In our study, majority of patients were from the group of Normal Glucose Tolerance (40%). Rest of the patients were equally distributed among the other two groups.

SEX DISTRIBUTION

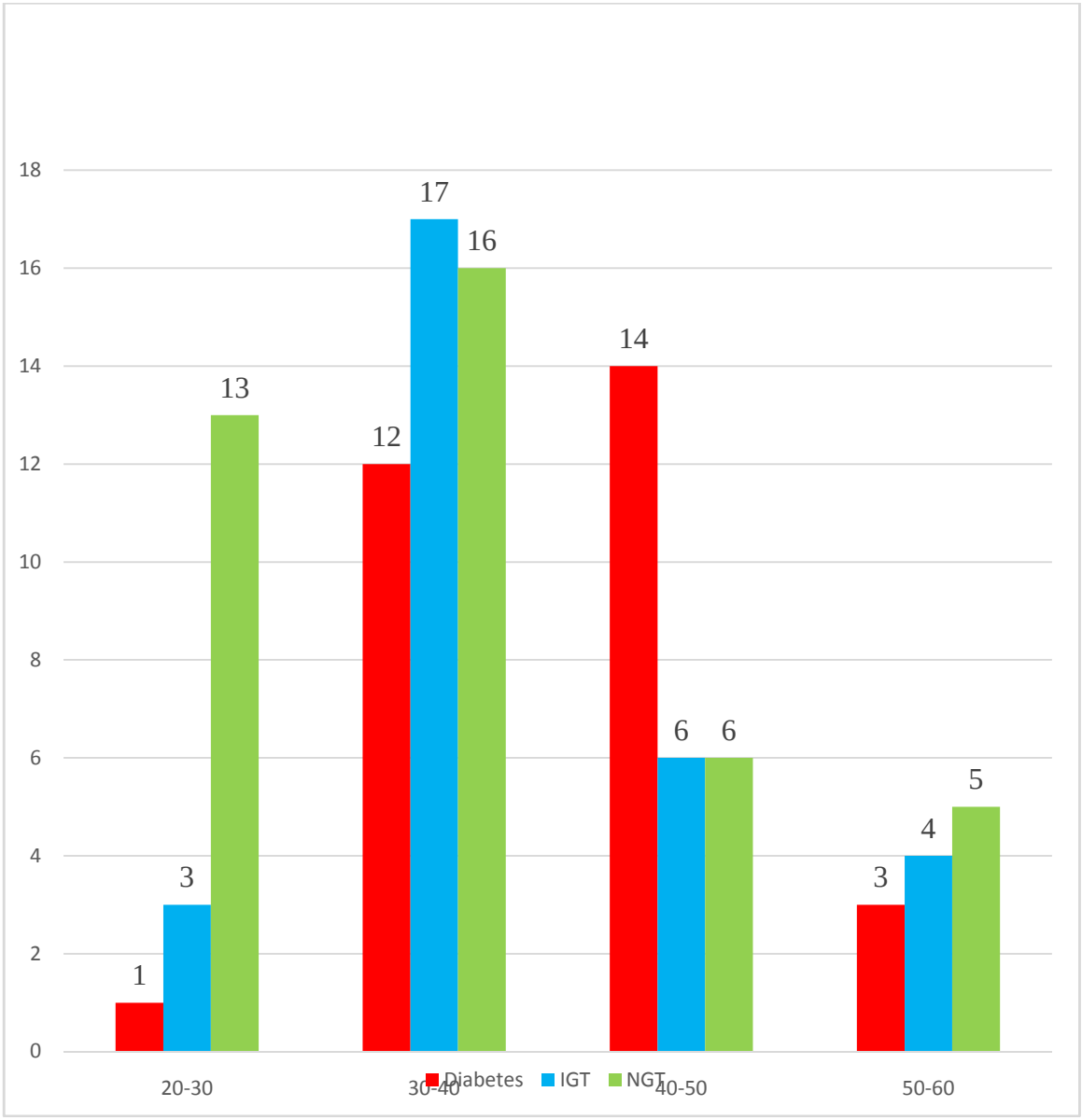


SEX - WISE DISTRIBUTION OF DIABETES, IGT, NGT

SEX	DIABETES	IGT	NGT	TOTAL
Male	10	9	9	28
Female	20	21	31	72
Total	30	30	40	100

In our study group females were 72% and males were 28%. There is a female preponderance in our study since, connective tissue disorders are more common in female population.

AGE -WISE DISTRIBUTION OF DIABETES, IGT, NGT



IGT - Impaired Glycemic Tolerance

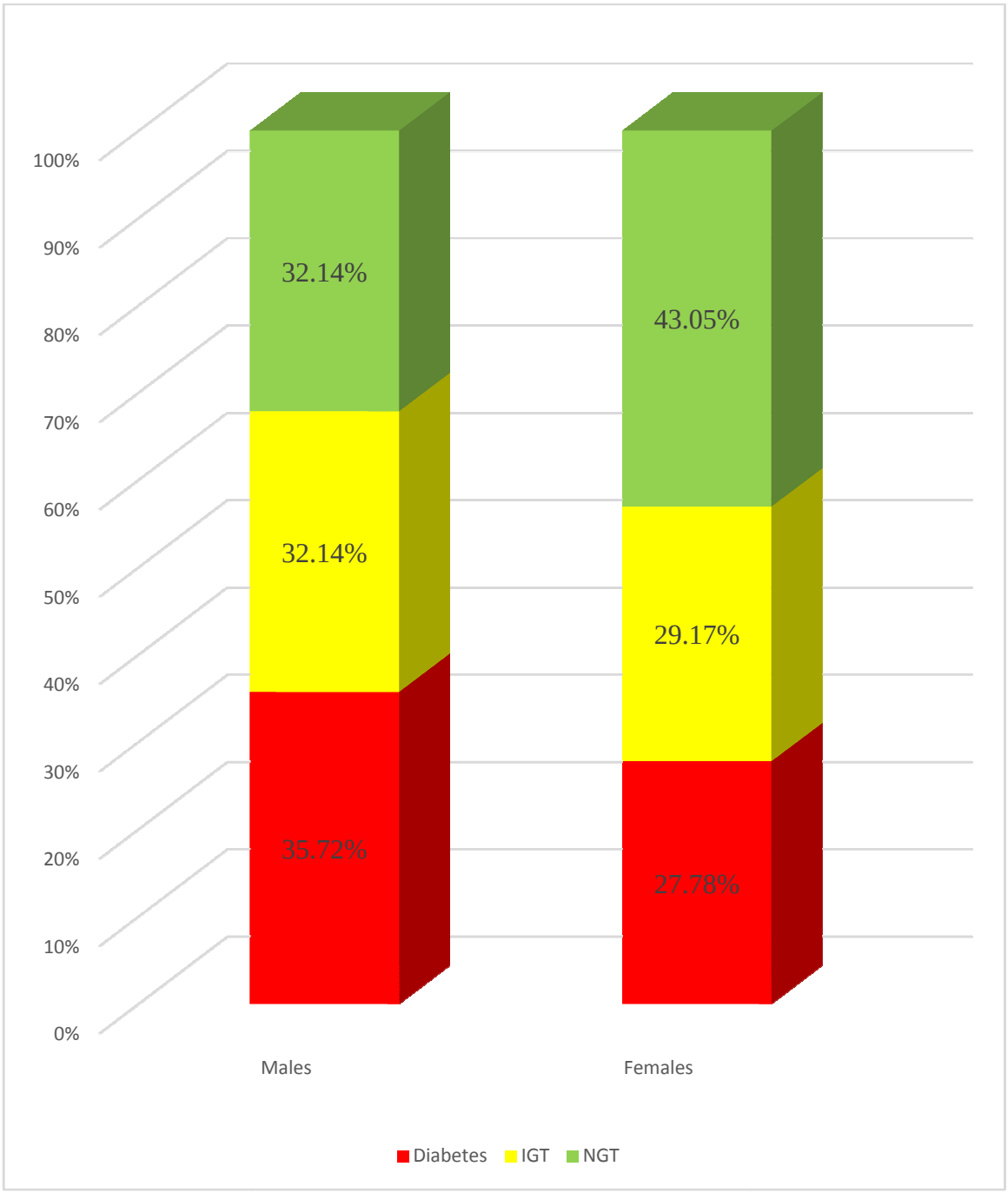
NGT - Normal Glycemic Tolerance

AGE -WISE DISTRIBUTION OF DIABETES, IGT, NGT

Age group (yrs.)	Diabetes	IGT	NGT	Total
20-30	1	3	13	17
30-40	12	17	16	45
40-50	14	6	6	26
50-60	3	4	5	12
Total	30	30	40	100

In our study group of 100 patients, clustering of cases were seen in the 30 - 50 yrs age group (71%). Of this 30 - 40 yrs group had maximum percentage (45%) in the study population. The oldest patient was 59 years old and the youngest 26 years old.

DISTRIBUTION OF DIABETES, IGT AND NGT AMONG MALES AND FEMALES

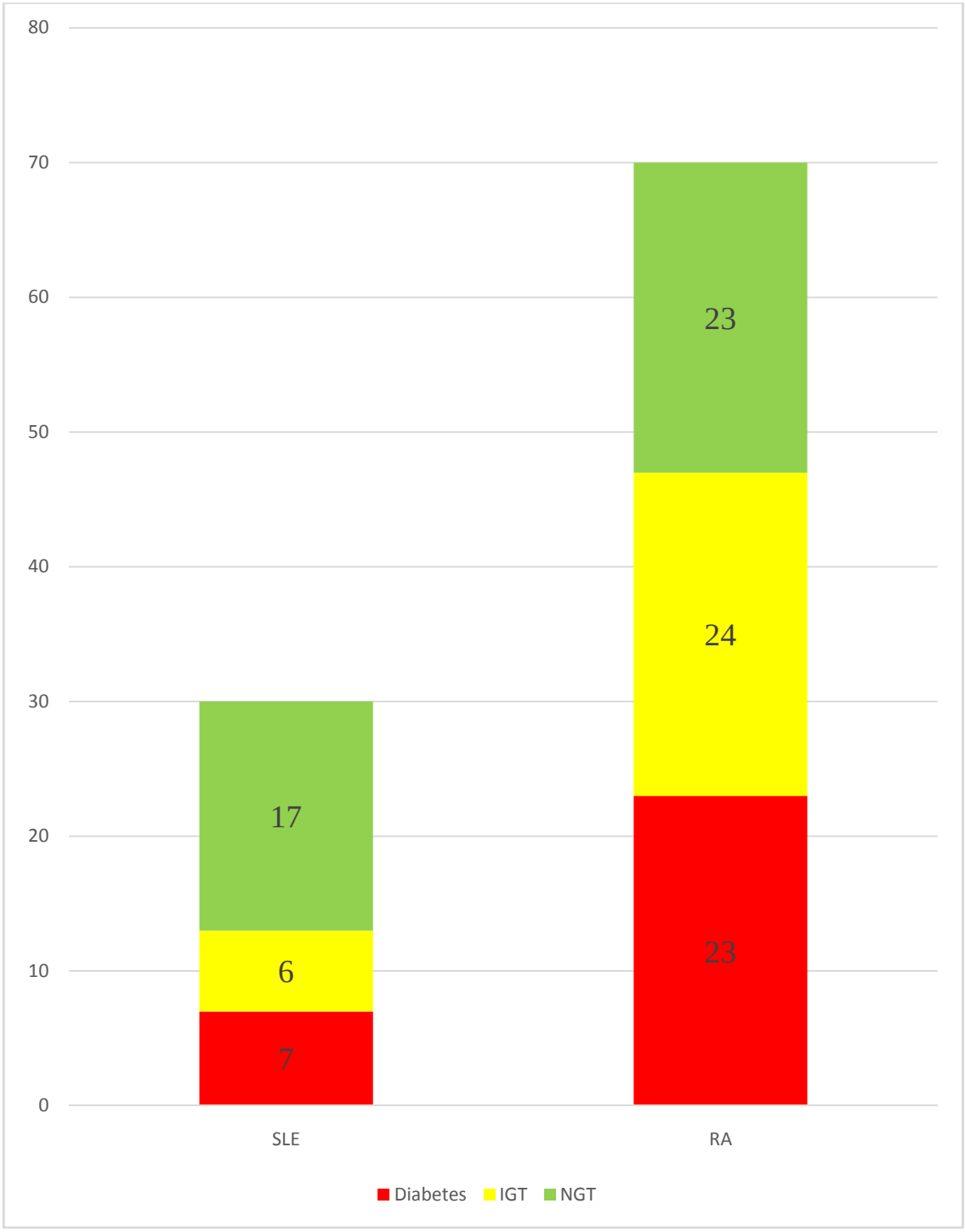


DISTRIBUTION OF DIABETES, IGT AND NGT AMONG MALES AND FEMALES

Glycemic status	Males		Females	
Diabetes	10	35.72%	20	27.78%
IGT	9	32.14%	21	29.17%
NGT	9	32.14%	31	43.05%

In our study majority of females were from the group of Normal Glucose Tolerance (43.05%). Males were equally distributed in all the three groups.

GLYCEMIC PROFILE OF SYSTEMIC LUPUS ERYTHEMATOSUS AND RHEUMATOID ARTHRITIS



GLYCEMIC PROFILE OF SYSTEMIC LUPUS ERYTHEMATOSUS AND RHEUMATOID ARTHRITIS

	Diabetes	IGT	NGT	Total
SLE	7	6	17	30
RA	23	24	23	70
Total	30	30	40	100

In our study group, majority of patients with Systemic Lupus Erythematosus belonged to the group of Normal Glucose Tolerance. Patients with Rheumatoid Arthritis were equally distributed in all the three group.

Analysis of HbA1c in Diabetes group

Paired Samples Statistics

	Mean	N	Std. Deviation	Std. Error Mean
PreHCQHbA1c	6.749	55	1.1202	0.1510
PostHCQHbA1c	6.387	55	.9524	0.1284

Paired Samples Correlations

	N	Correlation	Sig.
PreHCQHbA1c & PostHCQHbA1c	55	0.996	0.000

Paired Samples Test

	Paired Differences					T	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
PreHCQHbA1c - PostHCQHbA1c	0.3618	0.1939	0.0261	0.3094	0.4142	13.840	54	0.000

In the study group containing Diabetes patients, HbA1c obtained after 3 months of treatment with Hydroxychloroquine is compared with the baseline value. The results are analysed using paired t test. **The p value obtained is 0.001 and is highly significant**.

Analysis of HbA1c in IGT group

Paired Samples Statistics

	Mean	N	Std. Deviation	Std. Error Mean
PreHCQHbA1c	6.242	100	1.0529	0.1053
PostHCQHbA1c	5.952	100	0.8839	0.0884

Paired Samples Correlations

	N	Correlation	Sig.
PreHCQHbA1c & PostHCQHbA1c	100	0.993	0.000

Paired Samples Test

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
PreHCQHbA1c - PostHCQHbA1c	0.2900	0.2028	0.0203	0.2498	0.3302	14.303	99	0.000

In the study group containing Impaired Glucose Tolerance patients, HbA1c obtained after 3 months of treatment with Hydroxy chloroquine is compared with the baseline value. The results are analysed using paired t test. **The p value obtained is 0.001 and is highly significant**.

Analysis of HbA1c in NGT group

Paired Samples Statistics

	Mean	N	Std. Deviation	Std. Error Mean
PreHCQHbA1c	6.242	100	1.0529	0.1053
PostHCQHbA1c	5.952	100	0.8839	0.0884

Paired Samples Correlations

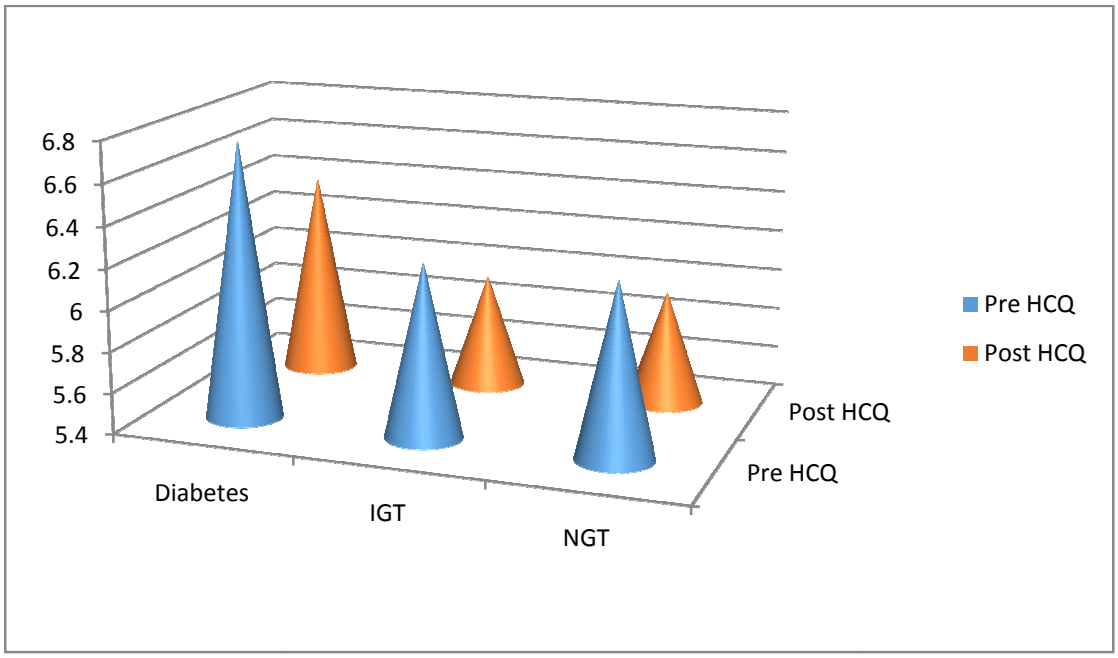
	N	Correlation	Sig.
PreHCQHbA1c & PostHCQHbA1c	100	0.993	0.000

Paired Samples Test

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
PreHCQHbA1c - PostHCQHbA1c	0.2900	0.2028	0.0203	0.2498	0.3302	14.303	99	0.000

In the study group containing Normal Glucose Tolerance patients, HbA1c obtained after 3 months of treatment with Hydroxy chloroquine is compared with the baseline value. The results are analysed using paired t test. **The p value obtained is 0.001 and is highly significant**.

COMPARISON OF HbA1c IN ALL THREE GROUPS



Analysis of FBS in Diabetes group

Paired Samples Statistics

	Mean	N	Std. Deviation	Std. Error Mean
PreHCQFBS	147.164	55	31.6852	4.2724
PostHCQFBS	136.745	55	27.0885	3.6526

Paired Samples Correlations

	N	Correlation	Sig.
PreHCQFBS & PostHCQFBS	55	0.994	0.000

Paired Samples Test

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
PreHCQFBS - PostHCQFBS	10.4182	5.6131	0.7569	8.9007	11.9356	13.765	54	0.000

In the study group containing Diabetes patients, FBS obtained after 3 months of treatment with Hydroxychloroquine is compared with the baseline value. The results are analysed using paired t test. **The p value obtained is 0.001 and is highly significant**.

Analysis of FBS in IGT group

Paired Samples Statistics

	Mean	N	Std. Deviation	Std. Error Mean
PreHCQFBS	132.810	100	29.8527	2.9853
PostHCQFBS	124.370	100	25.1523	2.5152

Paired Samples Correlations

	N	Correlation	Sig.
PreHCQFBS & PostHCQFBS	100	.992	.000

Paired Samples Test

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
PreHCQFBS - PostHCQFBS	8.4400	5.8626	0.5863	7.2767	9.6033	14.396	99	0.000

In the study group containing Impaired Glucose Tolerance patients, HbA1c obtained after 3 months of treatment with Hydroxychloroquine is compared with the baseline value. The results are analysed using paired t test. **The p value obtained is 0.001 and is highly significant**.

Analysis of FBS in NGT group

Paired Samples Statistics

	Mean	N	Std. Deviation	Std. Error Mean
PreHCQFBS	132.810	100	29.8527	2.9853
PostHCQFBS	124.370	100	25.1523	2.5152

Paired Samples Correlations

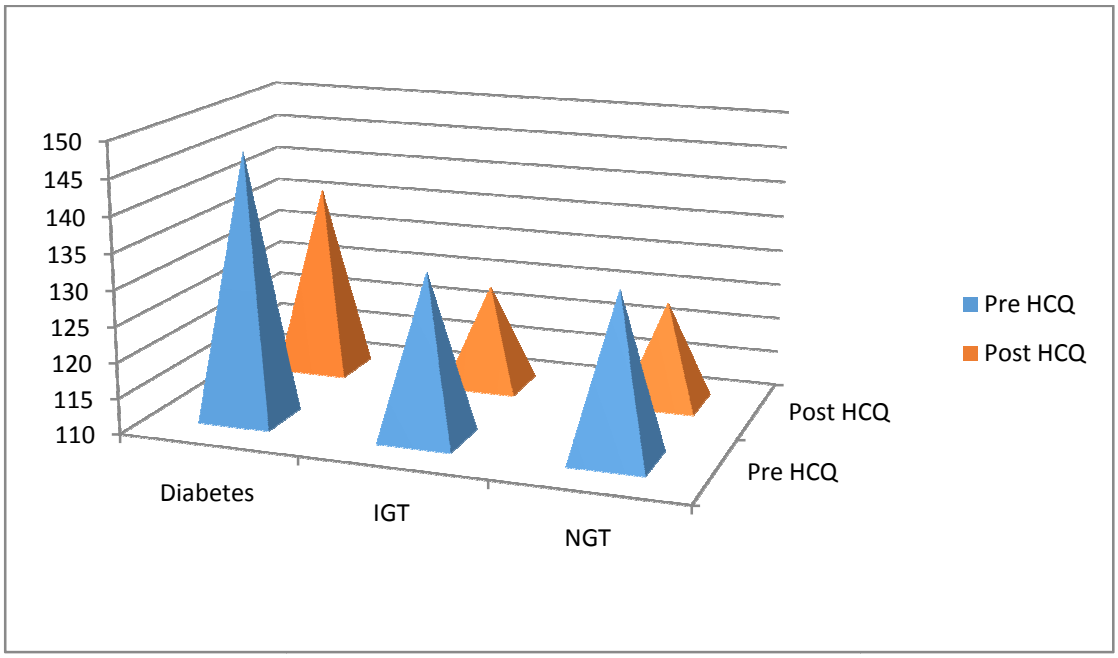
	N	Correlation	Sig.
PreHCQFBS & PostHCQFBS	100	.992	.000

Paired Samples Test

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
PreHCQFBS - PostHCQFBS	8.4400	5.8626	0.5863	7.2767	9.6033	14.396	99	0.000

In the study group containing Normal Glucose Tolerance patients, HbA1c obtained after 3 months of treatment with Hydroxy chloroquine is compared with the baseline value. The results are analysed using paired t test. **The p value obtained is 0.001 and is highly significant**.

COMPARISON OF FBS IN ALL THREE GROUPS



Analysis of PPBS in Diabetes group

Paired Samples Statistics

	Mean	N	Std. Deviation	Std. Error Mean
PreHCQPPBS	213.109	55	43.8966	5.9190
PostHCQPPBS	206.909	55	29.8870	4.0300

Paired Samples Correlations

	N	Correlation	Sig.
PreHCQPPBS & PostHCQPPBS	55	0.701	0.000

Paired Samples Test

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
PreHCQPPBS - PostHCQPPBS	6.2000	31.3170	4.2228	-2.2662	14.6662	1.468	54	0.148

In the study group containing Diabetes patients, PPBS obtained after 3 months of treatment with Hydroxychloroquine is compared with the baseline value. The results are analysed using paired t test. **The p value obtained is 0.148 and is not significant**.

Analysis of PPBS in IGT group

Paired Samples Statistics

	Mean	N	Std. Deviation	Std. Error Mean
PreHCQPPBS	200.120	100	37.5847	3.7585
PostHCQPPBS	196.150	100	25.9943	2.5994

Paired Samples Correlations

	N	Correlation	Sig.
PreHCQPPBS & PostHCQPPBS	100	.728	.000

Paired Samples Test

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
PreHCQPPBS - PostHCQPPBS	3.9700	25.7931	2.5793	-1.1479	9.0879	1.539	99	0.127

In the study group containing Normal Glucose Tolerance patients, PPBS obtained after 3 months of treatment with Hydroxy chloroquine is compared with the baseline value. The results are analysed using paired t test. **The p value obtained is 0.127 and is not significant**.

Analysis of PPBS in NGT group

Paired Samples Statistics

	Mean	N	Std. Deviation	Std. Error Mean
PreHCQPPBS	200.120	100	37.5847	3.7585
PostHCQPPBS	196.150	100	25.9943	2.5994

Paired Samples Correlations

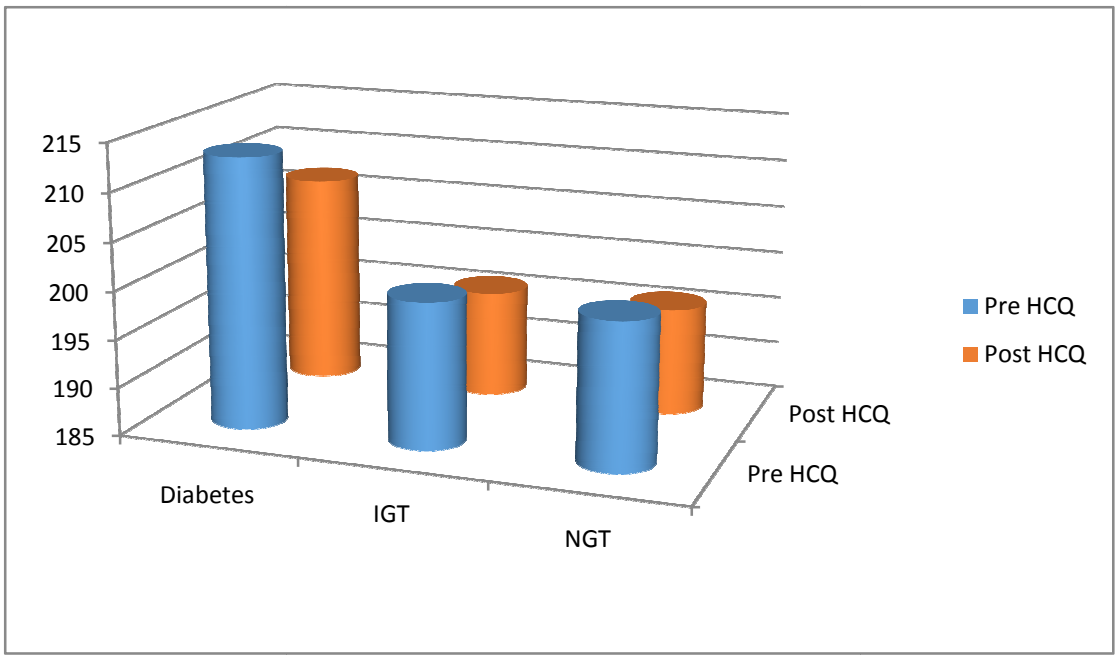
	N	Correlation	Sig.
PreHCQPPBS & PostHCQPPBS	100	.728	.000

Paired Samples Test

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
PreHCQPPBS - PostHCQPPBS	3.9700	25.7931	2.5793	-1.1479	9.0879	1.539	99	0.127

In the study group containing Normal Glucose Tolerance patients, PPBS obtained after 3 months of treatment with Hydroxy chloroquine is compared with the baseline value. The results are analysed using paired t test. **The p value obtained is 0.127 and is not significant**.

COMPARISON OF PPBS IN ALL THREE GROUPS



12.Descriptives

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
HbA1c - Before Therapy	100	5.0	8.8	6.242	1.0529
FBS - Before Therapy	100	97	206	132.810	29.8527
PPBS - Before Therapy	100	120	280	200.120	37.5847
Valid N (listwise)	100				

13. Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
HbA1c - After Therapy	100	5.0	8.1	5.952	0.8839
FBS - After Therapy	100	97	186	124.370	25.1523
PPBS - After Therapy	100	141	260	196.150	25.9943
Valid N (listwise)	100				

Mean value of HbA1c before Hydroxychloroquine therapy - 6.242

Mean value of HbA1c after Hydroxychloroquine therapy - 5.952

Mean value of FBS before Hydroxychloroquine therapy- 132.810

Mean value of FBS after Hydroxychloroquine therapy - 124.370

Mean value of PPBS before Hydroxychloroquine therapy - 200.120

Mean value of PPBSafter Hydroxychloroquine therapy - 196.150

DISCUSSION

DISCUSSION

An observational study was conducted in Institute of Rheumatology at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai - 600003 for a period of 6 months.

100 patients who are newly started on Hydroxychloroquine therapy for their rheumatological illness fulfilling both inclusion and exclusion criteria are chosen.In the study population females were 72 and males were 28. 70 patients had Rheumatoid arthritis and 30 of them had Systemic lupus erythematosus.

Routine investigations were taken. Serum glycated hemoglobin was determined using high performance liquid chromatography. Fasting blood sugar was measured after overnight fasting of 8 hours and Postprandial blood sugar was measured 2 hours after breakfast. All these investigations are done before starting the patient on Hydroxychloroquine. The patient is then started on Tablet Hydroxychloroquine 200 mg twice daily for their rheumatological illness.

The patients are then reviewed after 3 months of treatment. The same parameters are measured again at the end of 3 months. The results are then analysed using paired t test.

Pareek A, Chandurkar N, Thomas N, et al. conducted a double - blind, double - dummy, randomized, comparative, multicenter study in 15 centers across India between December 2009 and July 2013 on 267 uncontrolled type 2 diabetes patients, post 3 months treatment with glimepiride/gliclazide and metformin.

Hydroxychloroquine was started on 400 mg daily for 6 months. The efficacy was assessed at 12 weeks and 24 weeks by measuring HbA1c, Fasting blood sugar and Postprandial blood sugar. At the end of 12 weeks and 24 weeks all the three parameters reduced significantly from the baseline values. At the end of 12 weeks and 24 weeks the reduced values were HbA1c - 0.56% & 0.87%, FBS - 17 mg/dl & 14.22 mg/dl, PPBS - 34.74 mg/dl & 31.86 mg/dl respectively. The result was compared with another set of patients started on pioglitazone. The results were compared and was found to be nonsignificant.

Laura R. Rekedal, Elena Massarotti, Rajesh Garg et al. conducted a study in which 45 patients taking Hydroxychloroquine and 37 patients taking Methotrexate for Rheumatoid arthritis were chosen. HbA1c was measured at baseline and after 12 months after starting the treatment. The mean reduction in HbA1c from the pretreatment values was 0.66% in the Hydroxychloroquine and 0.11% in the Methotrexate receiving patients.

In our study 100 patients were divided into 3 groups based on the American Diabetes Association definition of Diabetes into Diabetes, Impaired glucose Tolernce and Normal Glucose Tolerance.

At the end of 3 months mean decrease in HbA1c was 0.362, 0.29 and 0.29% in Diabetes, Impaired glucose tolerance and Normal glucose tolerance patients respectively. **All of them had a p value of 0.001 and was highly significant.**

At the end of 3 months mean decrease in Fasting blood sugar was 10.42 mg/dl, 8.44 and 8.44 mg/dl in Diabetes, Impaired glucose tolerance and Normal glucose tolerance patients respectively. **All of them had a p value of 0.001 and was highly significant.**

At the end of 3 months mean decrease in Postprandial blood sugar was 6.2 mg/dl, 3.97and 3.97 mg/dl in Diabetes, Impaired glucose tolerance and Normal glucose tolerance patients respectively. **The p value in Diabetes, patients, Impaired glucose tolerant and Normal glucose tolerant patients were 0.148, 0.127 and 0.127 respectively and were not significant.**

LIMITATIONS

LIMITATIONS OF THE STUDY:

1. A multicentric study with a larger population is required to confirm the efficacy of Hydroxychloroquinein decreasing blood glucose.

2. All the patients were receiving Tablet Prednisolone 30 mg per day. The effect of the steroid in glucose homeostasis has to be taken into account.

3. Anemia, Hemoglobin S, Uremia and Pregnancy cause change decrease in the level of HbA1c.

CONCLUSION

CONCLUSION

- HbA1c decreased in all the three group of patients. The decrease was greatestamong Diabetics and same among Impaired and Normal glucose tolerant patients.

- Fasting blood sugar decreased in all the three group of patients. The decreasewas greatest among Diabetics and same among Impaired and Normal glucose tolerant patients.

- Postprandial blood sugar decreased in all the three group of patients. The decrease was greatest among Diabetics and same among Impaired and Normal glucose tolerant patients.

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BIBLIOGRAPHY

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ANNEXURES

PROFORMA

NAME OF THE PATIENT :

AGE / SEX :

IP/OP NUMBER :

OCCUPATION :

ADDRESS :

CONTACT NUMBER :

COMPLAINTS :

PAST HISTORY:

DM	
SHT	
CKD	
CAD	
COPD	
SLE	
RA	
SS	

TREATMENT HISTORY :

DRUG ALLERGY :

GENERAL EXAMINATION :

VITALS :

SYSTEMIC EXAMINATION

CARDIOVASCULAR SYSTEM:

RESPIRATORY SYSTEM :

ABDOMEN :

CENTRAL NERVOUS SYSTEM:

COMPLETE HEMOGRAM:

LIVER FUNCTION TEST:

RENAL FUNCTION TEST:

DATE OF STARTING HYDROXYCHLOROQUINE:

DATE OF BASELINE GLYCEMIC PROFILE:

DATE OF FINAL GLYCEMIC PROFILE:

TOTAL DURATION :

COMPLIANCE :

SIDE EFFECTS :

ASSESSMENT :

Age	Gender	Comorbidity	Date	FBS	PPBS	HbA1 C
			Baseline			
			Final			

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.Mohamed Iliyas A.
Postgradaute MD(General Medicine)
Madras Medical College
Chennai 600 003

Dear Dr.Mohamed Iliyas A.,

The Institutional Ethics Committee has considered your request and approved your study titled **"Glycemic Profile of patients on Hydroxychloroquine " No.13052015.**

The following members of Ethics Committee were present in the meeting held on 12.05.2015 conducted at Madras Medical College, Chennai-3.

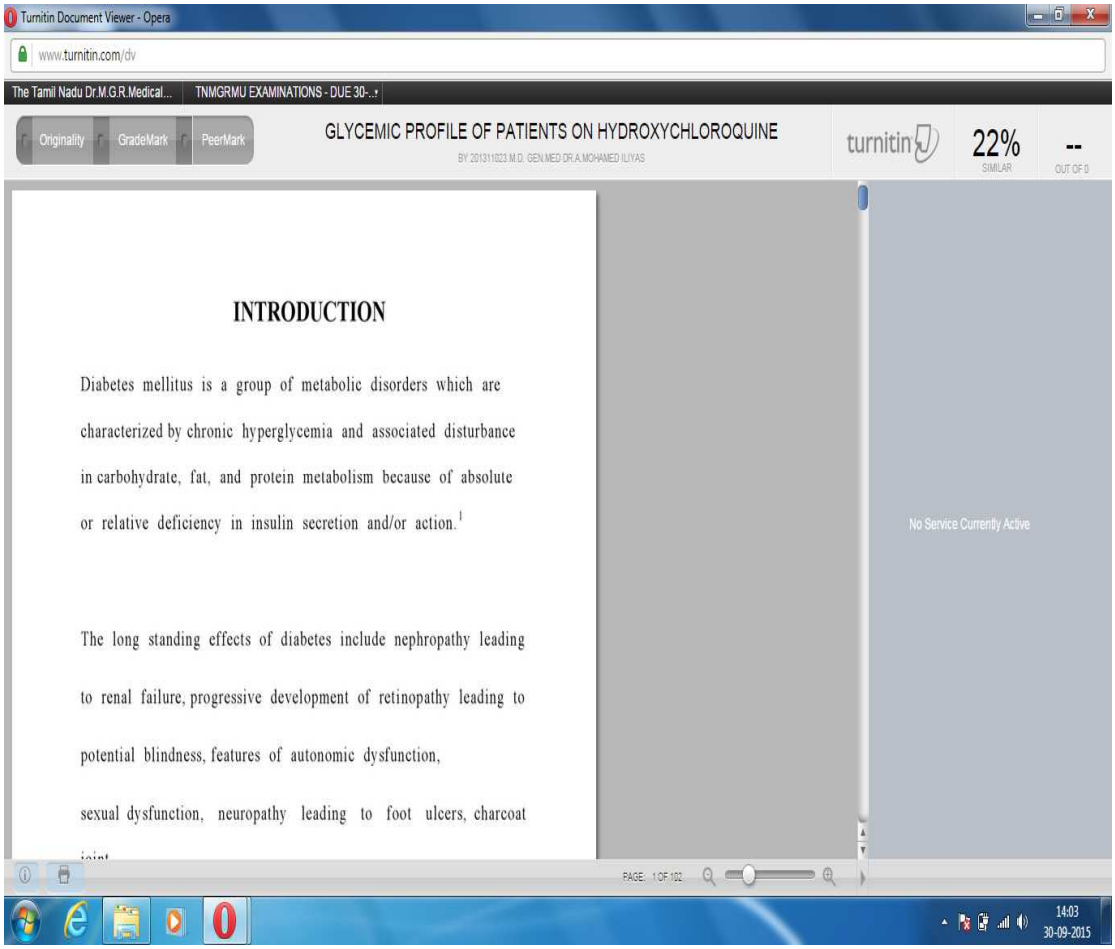
1. Prof.C.Rajendran, M.D.,	: Chairperson
2. Prof.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.B.Vasanthi, M.D., Prof. of Pharmacology, MMC	: Member
5. Prof.P.Ragumani, M.S., Professor of Surgery, MMC	: Member
6. Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
7. Prof.K.Srinivasagalu, M.D.,Director, I.I.M. MMC, Ch-3	: Member
8. Thiru S.Rameshkumar, B.Com., MBA	: Lay Person
9. Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
10. Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003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GLYCEMIC PROFILE OF PATIENTS ON HYDROXYCHLOROQUINE
BY 201311023 M.D. GEN.MED DR A.MOHAMED ILIYAS
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INTRODUCTION
Diabetes mellitus is a group of metabolic disorders which are characterized by chronic hyperglycemia and associated disturbance in carbohydrate, fat, and protein metabolism because of absolute or relative deficiency in insulin secretion and/or action.[1]
The long standing effects of diabetes include nephropathy leading to renal failure, progressive development of retinopathy leading to potential blindness, features of autonomic dysfunction,
sexual dysfunction, neuropathy leading to foot ulcers, charcoat
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INTRODUCTION

INFORMATION SHEET

We are conducting a study on **"GLYCEMIC PROFILE OF PATIENTS ON HYDROXYCHLOROQUINE"** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is to assess the efficacy of Hydroxychloroquine as an Oral Hypoglycemic Agent.

We are selecting certain cases and if you are found eligible, we may be using your blood samples to do certain tests which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of the investigator Signature of the participant

Date:
Place:

ஆராய்ச்சி தகவல் தாள்

சென்னை ராஜீவ்காந்தி அரசு பொது மருத்துவமனையின் பொது மருத்துவத்துறையில் "ஹைட்ராக்சி க்ளோரோக்யின் உட்கொள்ளும் நோயாளிகளின் இரத்த சர்க்கரை அளவை பரிசோதனை செய்தல்" நடைபெறுகிறது.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இதனால் தங்களது சிகிச்சையில் பாதிப்பு ஏற்படாது என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த ஆய்வில் தங்களுக்கு மருத்துவபரிசோதனை, இரத்தப் பரிசோதனை மற்றும் எக்ஸ்ரே (X-Ray) பரிசோதனை செய்யப்படும்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின்போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதை தெரிவித்துக்கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின்பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மை பற்றியும் ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின்போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள் :
இடம் :

CONSENT FORM

Study Detail	:	"GLYCEMIC PROFILE OF PATIENTS ON HYDROXYCHLOROQUINE"
Study Centre	:	Department of RHEUMATOLOGY, Rajiv Gandhi Government General Hospital, Chennai.
Patient's Name	:	
Patient's Age	:	
Identification Number	:	

Patient may check (☑) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ❑

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ❑

I hereby consent to participate in this study. ❑

I hereby give permission to undergo complete clinical examination , biochemical, immunological test. ❑

Signature of Investigator
Study Investigator's Name:

Signature/thumb impression
Patient's Name and Address:
DR.A. MOHAMED ILIYAS

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சியின் தலைப்பு

ஹைட்ராக்சி க்ளோரோக்யின் உட்கொள்ளும் நோயாளிகளின் இரத்த சர்க்கரை அளவை பரிசோதனை செய்தல்

ஆய்வு நிலையம் : பொது மருத்துவத்துறை,
சென்னை மருத்துவக் கல்லூரி சென்னை - 3.

பங்கு பெறுபவரின் பெயர் :

உள்நோயாளி எண் :

பங்குபெறுபவர் இதனை (✓) குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கின்றேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன், இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிகிறேன். ☐

இந்த இரு அறுவை சிகிச்சை முறைகளும் ஒப்புக்கொள்ளப்பட்ட முறைகள் என்பதையும் இதனால் உடலுக்கு எந்தவிதமான உபாதைகளும் இருக்காது என்பதை அறிந்துகொண்டு இந்த ஆய்வில் பங்குபெற முழு மனதுடன் சம்மதிக்கிறேன். ☐

பங்கேற்பவரின் கையொப்பம் ..... இடம்..... தேதி.....

இடது கை பெருவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் ..... இடம்..... தேதி.....

ஆய்வாளரின் பெயர் .....

MASTER CHART

AGE	SEX	DIAGNOSIS	DIABETES	IGT	NGT	Pre - HCQ HbA1c	Post - HCQ HbA1c	Pre - HCQ FBS	Post - HCQ FBS	Pre - HCQ PPBS	Post - HCQ PPBS
38	F	SLE	Y			7.5	7.1	169	157	244	232
49	F	RA	Y			7.9	7.4	180	166	253	241
53	M	RA			Y	5.4	5.3	109	106	183	180
41	F	SLE			Y	5.3	5.2	106	103	180	174
55	M	RA		Y		6.4	5.8	138	120	212	194
38	F	RA	Y			6.9	6.6	152	143	226	217
48	F	RA	Y			8.2	7.5	189	169	263	244
51	F	RA			Y	5.5	5.4	112	109	186	183
35	M	SLE			Y	5.5	5.4	112	109	186	183
57	F	RA	Y			8.5	7.7	198	174	272	247
36	F	RA			Y	5.4	5.3	109	106	183	180
47	M	RA	Y			7.7	7.2	174	160	247	235
27	F	SLE			Y	5.4	5.3	109	106	183	180
45	F	RA	Y			7.5	7.1	168	157	244	157
57	F	RA		Y		6.4	5.8	137	120	138	194
39	M	SLE	Y			6.8	6.5	149	141	223	141
26	F	RA			Y	5.2	5.2	103	103	174	174
55	F	RA			Y	5.3	5.3	106	106	180	180
48	M	RA	Y			7.7	7.2	174	160	247	235
35	F	SLE		Y		6	5.8	126	120	200	195
48	F	RA	Y			7.4	7	166	154	241	229
29	F	RA			Y	5	5	97	97	171	171
37	M	RA	Y			6.9	6.6	152	143	226	217
43	M	SLE			Y	5.1	5.1	100	100	174	174
46	F	RA	Y			7.7	7.3	174	163	247	163
58	M	RA		Y		6.4	5.8	137	120	212	194
57	F	SLE	Y			8.8	8.1	206	186	280	260
38	M	RA	Y			7.3	6.9	163	152	238	226
33	F	RA			Y	5.2	5.1	103	100	174	174
47	F	RA		Y		6.3	5.9	135	123	209	197
28	F	SLE			Y	5	5	97	97	171	171
39	M	RA	Y			7.2	6.8	160	149	235	223
38	F	RA			Y	5	5	97	97	171	171
49	F	RA	Y			8.6	7.9	200	180	274	253
38	M	RA		Y		6.2	5.8	132	120	206	194
34	M	SLE			Y	5.5	5.4	112	109	186	183
44	F	RA			Y	5.5	5.3	112	106	186	180
58	F	SLE			Y	5.2	5.1	103	100	177	174
48	F	RA	Y			7.6	7.1	171	157	244	232
39	F	SLE		Y		6	5.8	126	120	200	194
36	F	RA			Y	5.5	5.4	112	109	186	183
27	F	RA			Y	5.1	5.1	100	100	174	174
56	F	RA	Y			8.5	7.8	198	177	272	250

AGE	SEX	DIAGNOSIS	DIABETES	IGT	NGT	Pre - HCQ HbA1c	Post - HCQ HbA1c	Pre - HCQ FBS	Post - HCQ FBS	Pre - HCQ PPBS	Post - HCQ PPBS
37	M	RA		Y		6.1	5.9	129	123	203	197
33	M	RA			Y	5.2	5.1	103	100	177	174
48	F	SLE			Y	5.1	5	100	97	174	171
37	M	SLE	Y			7.2	6.7	160	146	235	220
38	F	RA		Y		6.3	5.9	135	123	209	197
29	F	RA			Y	5.4	5.3	109	106	183	180
34	F	SLE			Y	5.1	5	100	97	174	171
49	F	RA	Y			7.6	7.1	171	157	244	232
37	F	RA			Y	5	5	97	97	171	171
27	F	RA			Y	5.5	5.4	112	109	186	183
56	F	SLE		Y		6.4	5.8	138	120	138	194
48	F	RA		Y		6.3	5.9	135	123	209	197
36	M	RA			Y	5.3	5.1	106	100	180	174
39	F	RA	Y			8.4	7.7	195	174	269	247
28	F	SLE			Y	5.4	5.2	109	103	183	171
35	M	RA		Y		6.2	5.8	132	120	132	194
26	F	RA			Y	5.3	5.1	106	100	180	174
37	F	RA		Y		6.1	5.9	129	123	203	197
49	F	SLE	Y			7.8	7.3	177	163	250	238
35	F	SLE			Y	5.4	5.1	109	100	183	174
46	F	RA		Y		6.3	5.9	135	123	209	197
48	F	RA		Y		6.3	5.9	135	123	209	197
36	M	RA	Y			6.8	6.5	150	141	223	215
48	F	RA	Y			8.4	7.9	195	174	269	253
59	M	RA			Y	5.4	5.1	109	100	183	174
36	M	SLE		Y		6.1	5.9	129	123	203	197
28	F	RA			Y	5.5	5	112	97	186	171
47	F	SLE	Y			7.4	7	166	154	241	229
36	F	RA			Y	5.5	5.1	112	100	186	174
38	F	RA		Y		6.1	5.9	129	123	203	197
38	F	RA	Y			7.2	6.8	160	149	235	223
29	F	SLE			Y	5.5	5.4	112	109	186	183
46	F	RA		Y		6.3	5.9	135	123	209	197
29	F	SLE			Y	5	5	97	97	171	171
37	F	RA		Y		6.1	5.8	129	120	203	194
33	F	SLE			Y	5.1	5	100	97	174	171
37	M	RA	Y			6.8	6.5	150	141	223	215
47	M	RA		Y		6.3	5.9	135	123	209	197
36	F	RA		Y		6.1	5.9	129	123	203	197
27	F	RA			Y	5.4	5.1	109	100	183	174
37	M	RA		Y		6	5.8	126	120	200	194
32	F	SLE			Y	5.2	5	103	97	177	171
48	F	SLE	Y			8.6	7.9	188	180	262	253
29	F	RA		Y		5.9	5.7	123	117	197	191

AGE	SEX	DIAGNOSIS	DIABETES	IGT	NGT	Pre - HCQ HbA1c	Post - HCQ HbA1c	Pre - HCQ FBS	Post - HCQ FBS	Pre - HCQ PPBS	Post - HCQ PPBS
49	F	SLE			Y	5.2	5	103	97	177	171
33	F	RA			Y	5.3	5.2	106	103	180	177
27	M	SLE		Y		5.8	5.6	120	114	120	188
29	M	RA	Y			6.7	6.4	146	138	220	212
37	F	RA		Y		6	5.8	126	120	126	194
38	M	SLE			Y	5	5	97	97	171	171
38	F	RA	Y			7.5	7	169	154	244	229
28	F	RA		Y		5.8	5.6	120	114	120	188
45	M	RA			Y	5	5	97	97	171	171
36	F	RA		Y		6.2	5.8	132	120	132	194
38	F	SLE		Y		6	5.8	126	120	200	194
34	F	RA		Y		5.9	5.7	123	117	123	191
37	F	RA		Y		5.9	5.7	123	117	123	191